1

Epidemiology of Gynecologic Cancers

Louise A. Brinton
Robert N. Hoover

Disease-oriented texts often include a chapter on epidemiology or etiology, which is considered perfunctory if the book is used by therapists whose daily practice is rarely influenced by these considerations. This is not the case for physicians who treat patients with gynecologic cancers, because they have frequent opportunities to interpret epidemiologic findings and make observations of etiologic importance. Moreover, public health measures based on epidemiologic findings influence gynecologic practice perhaps more than any other clinical discipline. In particular, epidemiologic data are critical for the prevention and treatment of cervical and endometrial cancers.

From the observation 150 years ago of the rarity of cervical cancer in nuns to the most recent follow-up studies of type-specific human papillomavirus infection, the cause, natural history, and prevention of this disease have focused on sexual practices and suspect infectious agents. Screening interventions based on natural history studies have fundamentally altered the usual presentation of this disease, and as more information about preceding infectious processes becomes available, even more radical changes in presentation and management are probable.

The probable estrogenic cause of endometrial cancer was proposed by etiologically oriented gynecologists decades before its demonstration by epidemiologists. Unfortunately, this did not prevent the largest epidemic of iatrogenic cancer (i.e., endometrial cancer caused by estrogen replacement therapy) in recorded history. The resurgent interest in replacement therapy, effects of progestins added to this regimen, and associated risk-benefit questions are certain to link the epidemiologist and the gynecologist for the foreseeable future. The unexpected iatrogenic chemoprevention of endometrial and ovarian cancer through oral contraception has similarly thrust the two disciplines together around issues ranging from basic biology to risk-benefit assessments.

The rich tradition of the mingling of epidemiology and gynecologic oncology has led to better opportunities for prevention, screening, and insights into basic mechanisms of disease than for any other subspecialty concerned with cancer. This chapter is written with the aim of clarifying how epidemiology is an integral part of the effort to reduce the morbidity and mortality from cancer in women.

EPIDEMIOLOGIC CONCEPTS

In discussing the epidemiology of gynecologic cancers, results are summarized using the concept of ***relative risk***, a measure of association between a select factor and the occurrence of a particular cancer. These risks are considered relative because they refer to a risk compared with a standard, usually individuals who are not exposed to a particular factor. A relative risk of 2.0 indicates that an exposed individual has twice the risk of someone without exposure to this factor, and a relative risk of 0.5 indicates a risk half that of a nonexposed individual. Another way of expressing these risks is that there is a 100% increase or a 50% decrease in risk, respectively.

Often times, attempts are made to assess the confidence one can have that these risks represent truth, because in any epidemiologic study there is some measure of statistical uncertainty. A common way of expressing the range over which the relative risk could vary is the 95% confidence interval, which indicates the variation observed in 95 of 100 random samples of the population. If the lower limit (or upper limit in the case of reduced risk) of the confidence interval exceeds (or is less than) a relative risk of 1.0, the associated relative risk is considered statistically significant, or equivalent to a P value less than 0.05. Although the relative risk is our best estimate of magnitude of an association, the confidence interval gives the range over which we are 95% confident that the true relative risk lies, given the variability in estimates due to chance alone. With increases in the numbers of individuals in the sample population, the influence of chance becomes less, and the 95% confidence interval becomes more narrow around the point estimate of relative risk.

Relative risks are derived from two types of epidemiologic studies: prospective studies or retrospective studies (also called case-control studies). In *prospective studies*, a population is initially defined on the basis of exposure to a factor (e.g., menopausal estrogens). The population is followed over time to determine the incidence of disease among those exposed. This incidence is compared with that in a comparable nonexposed group. Without this specific information, comparisons are often made with rates of disease in the general population. The relative risk compares the incidence of disease in the exposed and unexposed groups.

Retrospective studies define populations on the basis of disease rather than exposure. In an endometrial cancer study, patients with endometrial cancer are identified, and their previous exposures to potential risk factors, which are determined through interviews, review of medical records, or other means, are compared with those of a similar group of nondiseased women. These studies can usually be conducted more quickly than prospective studies and can collect more information about potential risk factors, but it is important that appropriate groups are chosen for comparison and that associations do not merely reflect the influence of selective recall by diseased patients.

Prospective studies have the advantage of being able to examine relationships with a variety of diseases, but they are usually limited by the number of cases studied and by available information for potential risk factors. This presents problems in determining the independence of potential risk factors, because the goal of epidemiologic research is to derive unconfounded estimates of risk associated with a particular factor. For example, in determining the relationship of oral contraceptives and number of births to the risk of endometrial cancer, attempts must be made to control for the influence of each factor, because both are associated with each other and with the risk of disease. Attempts to examine the independence of effects can be achieved through statistical stratification or modeling of the data, which enable adjusted estimates of relative risk to be derived.

This chapter highlights associations derived from methodologically sound studies and presents estimates of risk that are unconfounded by other known risk factors. However, a problem for all epidemiologic studies is that confounding effects can only be evaluated for factors for which data have been collected. Thus, results must be cautiously interpreted, especially in deciphering cause and effect relationships. In assessing whether an association is causal, a variety of measures are used to determine the probability to which true biologic relationships may exist. These include the magnitude of the relative risk observed; the occurrence of dose-response relationships; concordance of results with other studies; and existence of readily defined biologic mechanisms for observed associations.

ENDOMETRIAL CANCER

Demographic Patterns

Cancer of the endometrium is the most common invasive gynecologic cancer and the fourth most frequently diagnosed cancer among American women today. An estimated 33,000 new cases were diagnosed in the United States in 1991.[4] The average annual age-adjusted (1970 U.S. standard) incidence from the Surveillance, Epidemiology and End Results (SEER) program, a cancer reporting system involving approximately 10% of U.S. residents, was 21.2 per 100,000 women for 1987; the corresponding age-adjusted mortality rate between 1984 and 1987 was 1.9 per 100,000 women, reflecting the relatively good prognosis for this cancer. The 5-year survival rate is approximately 85%, with a 92% survival rate for those diagnosed at an early stage. In 1991, it was calculated that approximately 4000 deaths from endometrial cancer occurred.[4]

Endometrial cancer rates are highest in North America and Northern Europe; intermediate in Israel, Southern Europe, and Latin America; and low in Asia and Africa.[161] The disease is rare before the age of 45, but the risk rises sharply among women in their late forties to middle sixties. The age-adjusted incidence for whites is approximately twice as high as for nonwhites, with reasons for the discrepancy remaining largely undefined (Fig. 1-1). Within the last several decades in the United States, a dramatic change in the incidence pattern for endometrial cancer has occurred, characterized by a marked increase that peaked about 1975 (Fig. 1-2).[226,233] Considerable evidence has linked this rise

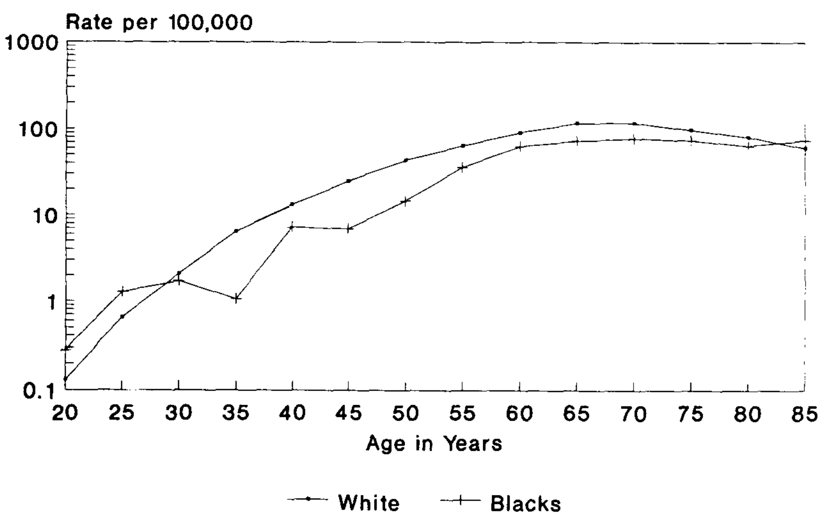

FIGURE 1–1. Age-specific incidence of endometrial cancer by race. (Data from the Surveillance, Epidemiology, and End Results Program, 1987.)

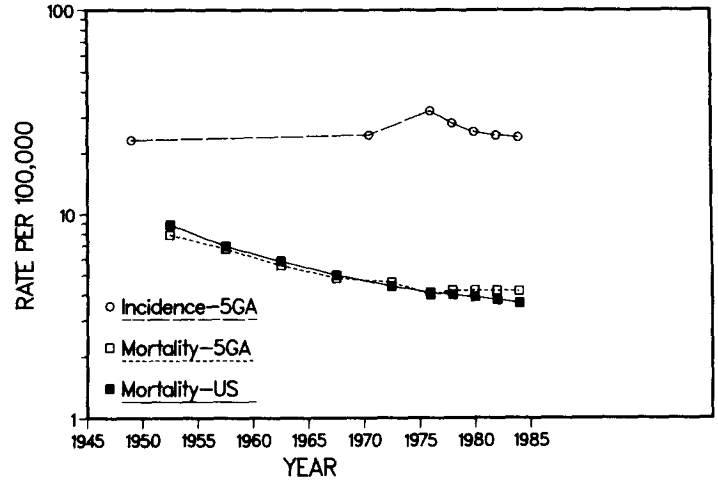

FIGURE 1–2. Incidence and mortality trends among U.S. white females for cancer of the corpus uteri. 5GA, five geographic areas. (Data from the Surveillance, Epidemiology, and End Results Program.)

and fall with the widespread use of estrogen replacement therapy in the late 1960s and early 1970s.

Temporal changes in endometrial cancer rates may be affected by several factors: the use of exogenous estrogens, hysterectomy rates (i.e., decreased number of women with uteri), the proportion of older women in the population (i.e., 75% of cases are diagnosed after 50 years of age), and changes in the prevalence of specific risk factors (e.g., obesity, nulliparity).[233] Recent reports show a continued decline in endometrial cancer incidence rates since 1979, despite an upswing in the use of menopausal estrogens to prevent osteoporosis and cardiovascular disease.[174] This may reflect the increased use since 1980 of progestins with estrogen replacement to offset the adverse effects of unopposed estrogens.

Reproductive and Menstrual Risk Factors

A recognized risk factor for endometrial cancer is nulliparity. Most studies demonstrate a threefold or greater excess risk for nulliparous than for parous women.[69,96,108,220] In most of these studies, the risk of endometrial cancer was found to decrease with increasing parity. There is some evidence that this effect may be more pronounced among premenopausal women.[96,135] Unlike breast cancer, the age at which a woman has her first liveborn child does not appear to relate to endometrial cancer risk.[69,96,116,135] In addition, breast feeding has not generally been related to endometrial cancer risk.[69,116,245]

It is possible that the association of nulliparity with elevated risk for endometrial cancer may reflect prolonged periods of infertility. The hypothesis that infertility is a risk factor for endometrial cancer is supported by studies showing higher risks for married nulliparous women than for unmarried women.[69,116] In two studies that specifically evaluated infertility as a risk factor for endometrial cancer, one found a nonsignificant elevation in risk, and the other found a 3.5-fold increase in risk for women who reported an inability to get pregnant for 3 or more years.[96,220]

Several biologic alterations linked to infertility have been associated with endometrial cancer risk, including anovulatory menstrual cycles (prolonged exposure to estrogens without sufficient progesterone); high serum levels of androstenedione (i.e., excess Δ-4 is available for conversion to estrone); and the absence of monthly sloughing of the endometrial lining (residual tissue may become hyperplastic). Another factor that may be important due to its effect on the amount of free estrogens is the level of serum sex hormone-binding globulin, which has been found to be lower in nulliparous than in parous women.[19]

Several studies found an excess of menstrual irregularities associated with the development of endometrial cancer. Amenorrhea leading to physician consultation was associated with a substantial excess risk of endometrial cancer in young women.[96] Wynder and others[245] noted an association of endometrial cancer risk with heavy menstrual bleeding and premenstrual breast swelling.

Early ages at menarche were related to elevated risk for endometrial cancer in several studies, although associations have generally been rather weak and trends inconsistent.[69,96,116,148,220] Several studies found stronger effects of age at menarche among younger women, although this has not been consistently demonstrated.[96,116,135]

The extent to which these relationships reflect increased exposure to ovarian hormones or other correlates of early menarche (e.g., increased body weight) is unresolved.

Most studies have indicated that the age at menopause is directly related to the risk of developing endometrial cancer.[69,116,245] About 70% of all women diagnosed with endometrial cancer are postmenopausal. Most studies support the estimate of MacMahon[149] that there is a 2.4-fold greater risk associated with natural menopause after the age of 52 than before age 49. Elwood and others[69] hypothesized that the effect of late age at menopause on risk may reflect prolonged exposure of the uterus to estrogen stimulation in the presence of anovulatory (progesterone deficient) cycles. The interrelationships among menstrual factors, age, and weight are complex, and the biologic mechanisms of these variables operating in the pathogenesis of endometrial cancer are subject to substantial speculation.

Hormones

ENDOGENOUS HORMONES

An excess endometrial cancer risk among young women has been noted for two conditions associated with abnormally high estrogen levels: Stein-Leventhal syndrome and estrogen-producing ovarian tumors.[70,72,84] Compared with controls, women with endometrial cancer have elevated levels of serum estrone and androstenedione, and in one study, these relationships persisted after adjustment for body mass.[9]

POSTMENOPAUSAL EXOGENOUS HORMONES

The relationship between exogenous hormones and risk of endometrial cancer has received considerable attention. Many studies found that any use of estrogen replacement therapy is associated with a 2-fold to 12-fold elevation in risk of endometrial cancer.[5,80,108,116,145,148,200,208,234] In most investigations, the increased risk was not observed unless the drugs were used for at least 2 to 3 years, and longer use of estrogens was generally associated with higher risk.[80,108,116,234] The highest relative risks have been observed after 10 years of use, reaching relative risks of approximately 10 to 20, although it is not clear whether there is any additional increase after 15 years.[234] In most studies, cessation of use appears to be associated with a relatively rapid decrease in risk, although several studies suggest that elevated risks may continue for some time after discontinuation.[108,116,148,200,234] There is some evidence that risk increases with estrogen dose, although this association has not been consistently observed.[5,80,108,116,145,148] The observation that risk is higher for continuous than for cyclic administration has not been confirmed in all studies.[5,108,145,148,234]

Assessment of effects of specific types of hormone preparations on endometrial cancer risk has been limited because most American women have been treated with the conjugated estrogen Premarin. Although there is evidence that nonconjugated estrogens, such as diethylstilbestrol (DES), increase risk, there is some suggestion that the effects of conjugated estrogens may be somewhat stronger than those of other estrogens, including estradiol.[5,175] A few studies indicate elevated risks associated with use of either injectable estrogens or vaginal hormone creams.[80,116] In addition, young women with gonadal dysgenesis (Turner's syndrome) treated with DES experience an excess risk of endometrial cancer.[144,239]

The associations of risk with estrogen replacement therapy are strongest among women who are thin, nondiabetic, and normotensive.[108,116,148,208] These findings suggest that estrogen metabolism differs in these groups of women or that risk is already high enough in obese, hypertensive, or diabetic women that exposure to exogenous estrogens has only a small additional effect.

An interesting observation is that tumors associated with estrogen use generally demonstrate favorable characteristics, including earlier stage at diagnosis, lower grade, and fewer instances of myometrial invasion.[5,80,108,116,145,148] Estrogen users also tend to be younger at diagnosis than patients who have not used estrogens, and the tumors are more frequently accompanied by hyperplasia or adenomyosis.[68,203] Although these observations may indicate that some advanced endometrial hyperplasias are being diagnosed as endometrial carcinomas, several studies and pathologic reviews have shown that the association of estrogen with endometrial cancer persists.[5,108,116] Although the estrogen-associated risk is highest for early-stage cancers, the elevated risks also pertain to later-stage disease.[190,200] Thus, misclassification of endometrial cancer probably accounts for only a small portion of the elevation in risk associated with estrogen use.

Despite considerable evidence linking estrogen use to an increased risk of endometrial cancer, several investigators have expressed skepticism about the association. The major concern, suggested to be a form of detection bias, postulates that estrogen-induced bleeding leads to a diagnosis of cancer among women who would otherwise remain asymptomatic, causing an overrepresentation of estrogen users in the case series and resulting in a falsely inflated risk associated with estrogen use. As evidence for this, Horwitz and Feinstein[105] cited the decline in risk within 1 to 2 years after cessation of estrogen use and the fact that estrogen use is most strongly associated with low-grade, minimally invasive lesions.

To demonstrate this bias empirically, Horwitz and Feinstein[105] conducted a case-control study using an alternative control series consisting of women admitted for a dilatation and curettage or a hysterectomy. A twofold relative risk was found for estrogen use when this group was compared with endometrial cancer cases, but a more conventional control group yielded a ratio of 12. However, this selection of a gynecologic control group, which is itself related to estrogen use, biased relative risks toward a finding of no association. Another argument against detection bias derives from findings by Hulka and others[108] that estrogen use was not associated with uterine bleeding in either cancer cases or a gynecologic control group, but only among dilatation and curettage controls, suggesting that the conventional design offers a more valid comparison. Detection bias could explain associations with estrogen use only if a sizable portion of endometrial cancer remains undiagnosed, but a necropsy study showed that this percentage is extremely small.[106] Moreover, if the association was simply the result of estrogens inducing bleeding in asymptomatic women, it would be unrelated to duration of use or perhaps more prominent in short-term users, but the association with endometrial cancer is strongest for long-term users. For these reasons, it seems improbable that detection bias can explain the observed associations of estrogen use with endometrial cancer.

Progesterone has been shown to produce regressive changes in endometrial hyperplasia, a presumed precursor of endometrial cancer.[173] Recently, there has been widespread enthusiasm for combining estrogen therapy with progestins to combat carcinogenic effects. There have been lower rates of endometrial hyperplasia among women receiving combined therapy than for those receiving estrogens alone.[235] The effect of combined therapy on the occurrence of endometrial cancer remains less clear. Gambrell and others[78] found that estrogen-progesterone users were at a lower risk of endometrial cancer than untreated women. However, the subjects were not randomized to treatment groups and the results were not adjusted for age or other recognized endometrial cancer risk factors. In three series of patients treated with exogenous estrogens, no cases of adenocarcinoma occurred among women who also received added progestins.[81,88,163] A Swedish study found that a two- to threefold excess risk associated with estrogens alone appeared to be counteracted by the addition of a progestin.[175] Because most estrogen usage in this cohort consisted of estradiol, further studies are needed to address whether similar advantages of added progestins apply to the more common usage of conjugated estrogens in the United States.

ORAL CONTRACEPTIVES

Further evidence for the role of exogenous hormones in the pathogenesis of endometrial cancer derives from studies that evaluated the effects of oral contraceptives. These studies demonstrated significantly higher risks in users of sequential oral contraceptives (i.e., containing a high dose of estrogen and a weak progestin) and significantly lower risks of endometrial cancer in women using estrogen-progestin combination pills.

With respect to sequential oral contraceptives, several studies have shown that women who used Oracon, a sequential preparation that employed dimethisterone (weak progestogen) with a large dose of a potent estrogen (ethinyl estradiol) had substantially elevated risks of endometrial cancer.[96,232] The risk associated with the use of other sequential oral contraceptives remains unclear, mainly because these drugs are no longer marketed.

In contrast, users of combination oral contraceptives have been found to experience approximately half the risk of nonusers, and long-term users in most studies experience even further reductions in risk.[42,96,107,113,116,232] Kaufman and others[113] showed that the reduced risk persisted for at least 5 years after discontinuation, but Weiss and Sayvetz[232] found that the protective effect waned within 3 years. In one study, the greatest reduction in risk was associated with high-progestin-dose pills, although this was not confirmed in another study.[96,107] In several studies, the protective effect of the pill appears greatest among nulliparous women.[42,96] In other studies, the protection has been limited to nonobese women or those who have not been exposed to noncontraceptive estrogens.[96,232]

Obesity

Obesity is a well-recognized risk factor for endometrial cancer, with as much as 25% of the disease possibly explained by this factor.[69,108,116,129,145,232] Very heavy women appear to have disproportionately high risks. Wynder and others[245] reported a ninefold excess risk for women 51 or more pounds above average weight. Although studies have demonstrated significant positive trends of endometrial cancer with both weight and various measures of obesity, including Quetelet's index (weight/height^2), height has not been consistently associated with risk. Obesity appears to affect both premenopausal and postmenopausal endometrial cancer.[116,135]

Blitzer and others[20] found a positive association between endometrial cancer and adolescent obesity, and hypothesized that long-standing obesity is a more important risk factor than adult weight. Wynder and others,[245] however, found that risk increased with weight at ages 50 to 59 years within each category of reported weight at ages 25 to 29. Endometrial cancer patients were heavier than average at both ages and gained more weight over time. Henderson and others[96] found that weight at age 18 was strongly associated with risk, although adjustment for current weight substantially reduced risk estimates. These studies suggest that later adult weight may be the most important risk factor.

Recent interest has focused on determining whether the distribution of body fat predicts endometrial cancer risk. Austin and others[9] found a positive independent effect of a high ratio of subcapular to triceps skinfold fat, a measure comparing central to peripheral obesity, and Elliott and others[66] reported that women with high ratios of waist to hip circumferences or those with more upper body fat were at increased risk. Folsom and others,[74] however, found no effect of waist-to-hip or trunk-to-limb ratios after adjustment for total body mass.

Dietary Factors

Despite the fact that obesity has been consistently related to endometrial cancer, few epidemiologic studies have evaluated the etiologic role of diet. Geographic differences in disease rates (i.e., high rates in Western and low rates in Eastern societies) suggest that nutrition has a role, especially the high content of animal fat in Western diets.[83] Armstrong and Doll[8] demonstrated a strong correlation between a country's total fat intake and endometrial cancer incidence.

Preliminary results from a case-control study of dietary intake (24-hour recall) and endometrial cancer risk showed that protein and total fat intake did not differ between study groups; however, carbohydrate intake and total energy (kcal) were higher among cancer cases than controls.[6] These data suggest that excess calories may be more important than fat in the development of endometrial cancer. However, a study by La Vecchia and others[129] found a significant positive trend in risk with increasing fat consumption, although no information was collected on total calorie intake.

Studies of vegetarians provide evidence that dietary factors may affect endometrial cancer risk through modifications in hormone metabolism.[6,7] Thus, postmenopausal vegetarian women have been found to have lower urinary levels of estriol and total estrogens, lower plasma prolactin levels, and higher serum values of sex hormone-binding globulin than nonvegetarians. These patterns could not be attributed to differences in body weight.

In one study, women who reported regular use of alcoholic beverages were at approximately a 45% reduced risk of endometrial cancer, with the effect most pronounced among overweight women, suggesting that alcohol may exert a protective effect by attenuating endogenous estrogen levels.[228] In another study, however, alcohol consumption was related to a nonsignificant elevation in risk, emphasizing the need for further evaluation of the relationship between alcohol consumption and endometrial cancer.[129]

Medical Conditions

Diabetics have elevated risks of endometrial cancer, which may reflect their higher serum levels of estrone.[69,108,129,149,220] It is unclear, however, whether the association with diabetes is independent of the correlated effects of age or obesity. In one study, an association with diabetes persisted after adjustment for weight and socioeconomic status, but it was restricted to recent diabetes diagnoses, suggesting the influence of detection bias.[69] Studies have not usually classified diabetics according to type.

Hypertension has also been associated with endometrial cancer, but the relationship has not been confirmed in all studies.[69,108,129,148,245] Positive findings may be partially explained by the correlation of hypertension with other factors, but at least one investigation found that the association between high blood pressure and endometrial cancer persisted even after obesity had been taken into account.[69]

A relationship between arthritis and endometrial cancer, observed in one study, was not confirmed in another.[69,116] Several studies have suggested a relationship of endometrial cancer risk with either previous thyroid disorders or gallbladder disease.[108,148,245] The extent to which these relationships reflect correlated effects of obesity remains unclear.

Other Risk Factors

Women of upper socioeconomic status have been reported to be at higher risk of endometrial cancer.[69,116] Findings related to socioeconomic status may be partially explained by other endometrial cancer risk factors correlated with affluence (e.g., overnutrition or use of estrogen replacement therapy).

A reduced risk of endometrial cancer among smokers has been reported, with current smokers having approximately half the risk of nonsmokers.[12,139,140,209,214,220] In most of these studies, a gradient of decreasing risk with increasing amounts smoked has been observed. Cigarette smoking has been linked to an earlier age at natural menopause in some populations and to alterations in endogenous estrogens, which may explain the inverse relationship between smoking and endometrial cancer, especially given findings that reduced risk associated with long-term smoking is more pronounced in postmenopausal than premenopausal women.[150] Several reports have found that the reduced risk associated with smoking is most apparent in high-risk women, including obese patients and those exposed to exogenous estrogens.[139,209]

Carcinogenesis

Epidemiologic, clinical, and laboratory data clearly show an influence of ovarian hormones on endometrial cancer risk. Estrogen is a potent growth-stimulating agent for endometrial tissue and has been shown to induce hyperplasia. Conversely, progesterone blocks estrogen-mediated growth and converts proliferative endometrium to secretory endometrium. Although the role of hyperplasia in the pathogenesis of endometrial cancer is unclear, it is generally believed that most endometrial cancers evolve through successive stages of hyperplasia, with adenomatous hyperplasia an early structural alteration. Thus, the biologically antagonistic effects of estrogen and progesterone on proliferation appear to be centrally involved in the epidemiology of endometrial cancer.[78,81]

A unified theory of how risk factors for endometrial cancer might operate through one common hormonal pathway has been suggested (Fig. 1-3). The "carcinogen" is estrogen, particularly estrogen not tightly bound to plasma protein and therefore more available for tissue binding. Progesterone blocks the carcinogenic effect of estrogen on the endometrium. Functional ovarian tumors, the Stein-Leventhal syndrome, late menopause, and administration of exogenous estrogens and sequential oral contraceptives produce higher levels of estrogen exposure without the compensatory effects of progesterone. Obesity could also contribute in a variety of ways.[120,202] Adipose tissue is the primary site for conversion of androstenedione (Δ-4) to estrone, the primary source for estrogen after menopause. Obesity is associated with higher conversion rates and/or elevated plasma levels of estrogen. In addition, obesity is related to lower levels of sex hormone–binding globulin and more frequent anovulatory menstrual cycles (less progesterone). Vegetarianism is associated with lower plasma estrogen levels, presumably on the basis of the relationship of diet composition to estrogen metabolism. The beneficial effects of combination oral contraceptives and cyclic progestins added to hormone replacement therapy presumably operate through the antiestrogen effects of progesterone. The peculiar age incidence patterns for endometrial cancer (i.e., extremely rare under age 45, followed by a rapid and progressive rise from ages 45 to 60) could also reflect the waning influence of progesterone. Nulliparity, hypertension, diabetes, and race may yet be added to this unifying scheme as our knowledge of endocrinology increases.

Although there are several identified risk factors for endometrial cancer (Table 1-1), important gaps in our knowledge (Fig. 1-3) inhibit a full understanding of the proposed carcinogenic process. We need to understand the influence of when in a woman's life obesity matters most; the influence of weight loss; whether the number of adipocytes, their fat composition, or

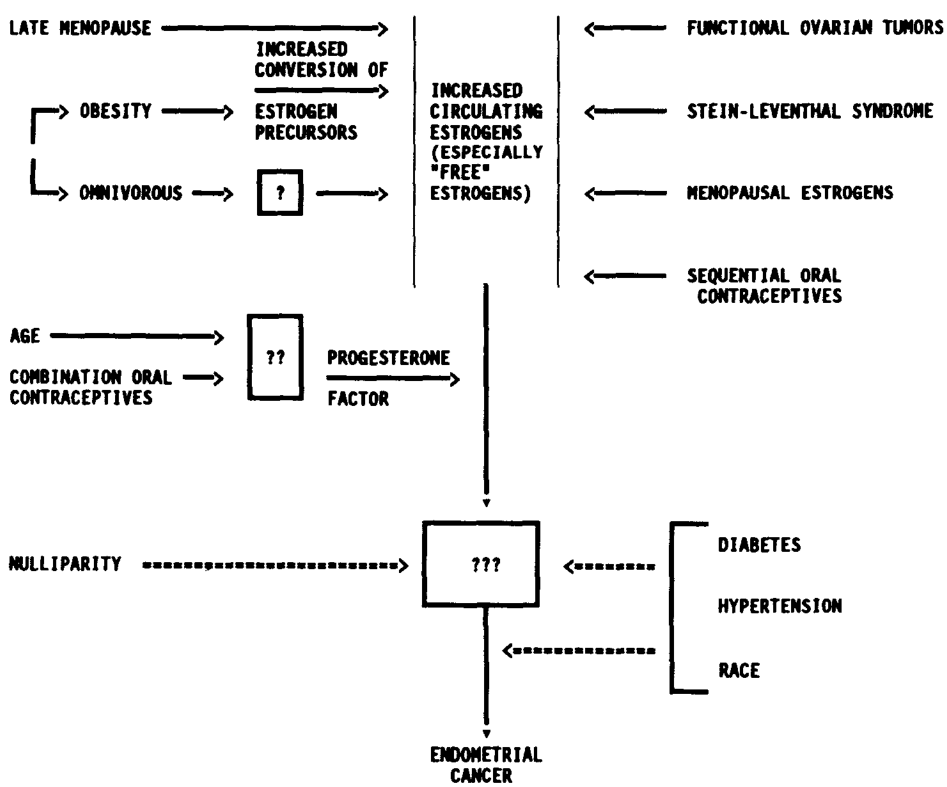

FIGURE 1–3. Risk factors for endometrial cancer and their possible modes of action.

TABLE 1–1.
Risk Factors for Endometrial Cancer

Factors Influencing Risk	Estimated Relative Risk*
Older ages	2–3
Residency in North America, Northern Europe	3–18
Higher levels of education or income	1.5–2
White race	2
Nulliparity	3
History of infertility	2–3
Menstrual irregularities	2
Early ages at menarche	1.5–2
Late ages at natural menopause	2–3
Long-term use or high dosages of menopausal estrogens	10–20
Use of oral contraceptives	0.3–0.5
Obesity	2–5
Stein-Leventhal disease or estrogen-producing tumors	>5
Histories of diabetes, hypertension, gallbladder disease, or thyroid disease	1.5–3
Cigarette smoking	0.5

**Relative risks depend on the study and referent group employed.*

other factors determine peripheral conversion of androstenedione; and the precise hormonal mechanisms associated with vegetarianism. Perhaps the most important gap is in understanding the basic mechanism of estrogen carcinogenesis. Are estrogens complete carcinogens? Are they classic "promoters," promoting already initiated cells, or do they operate by stimulating growth and offering greater opportunity for abnormal cells to arise or for carcinogens to act on vulnerable genetic material? The epidemiologic data are consistent with estrogens acting at a relatively late stage of carcinogenesis. If this supports their position as tumor promoters, no initiators of the process have yet been identified.

OVARIAN CANCER

Demographic Patterns

Approximately 1 in 70 American women will develop ovarian cancer during their lifetimes, with this cancer accounting for 4% of all cancers in women. The average annual age-adjusted incidence for all SEER areas during 1987 was 13.7 per 100,000 women, and an estimated 20,700 new cases of ovarian cancer were diagnosed in the United States in 1991.[4] A relative survival rate of 85% can be achieved if ovarian cancer is diagnosed early, but unfortunately the disease is usually not detected until it has reached an advanced stage, which imposes a high fatality rate.[4] The 5-year survival rate for ovarian cancer is approximately 38%, and the average annual age-adjusted mortality rate is 7.7 per 100,000 women. Ovarian cancer ranks fourth as a cause of death among cancers in females; in 1990, an estimated 12,400 women in the United States died from ovarian cancer.[4]

Ovarian cancer rates are high in North America and Northern Europe and low in Japan.[161] White females had considerably higher rates of ovarian cancer than blacks (Fig. 1-4), but there is some evidence that this difference may be narrowing.[61]

Reproductive Variables

Gravidity is associated with a decreased ovarian cancer risk.[21,95,110,244] Compared with nulligravidous women, women with a single pregnancy have a relative risk of 0.6 to 0.8, with each additional pregnancy lowering risk by about 10% to 15%. This derives primarily from associations with number of full-term births, although in several studies, risk has also been found to decrease with increasing number of incomplete pregnancies.

Some studies have reported an increased risk of ovarian cancer associated with late ages at first pregnancy, but the inverse correlation between age at first pregnancy and number of pregnancies makes it necessary to consider both effects simultaneously.[130] In most studies that have adjusted effects of age at first pregnancy for number of pregnancies, no residual effect of age at pregnancy persists.[95,103,110,147,164,224]

Most studies that have evaluated breastfeeding have not found it to be a risk factor for ovarian cancer, although several

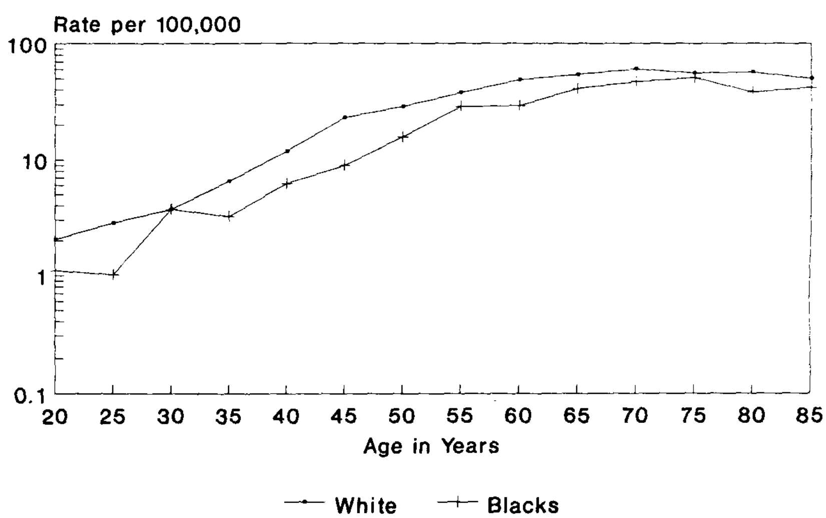

FIGURE 1–4. Age-specific incidence of cancer of the ovary by race. (Data from the Surveillance, Epidemiology, and End Results Program, 1987.)

studies have shown some reduction in risk.[21,95,183] However, trends with months of breastfeeding have been lacking, although this may have been due to the lack of a strong correlation between duration of breastfeeding and suppression of ovulation.

Whether the relationship of risk to pregnancy history reflects a hazardous role for infertility or a protective role for pregnancy is unclear. Supporting a role for abnormal endocrine factors are studies that have shown higher risks among infertile women.[95,110,147,164,237] In the study of Booth and others,[21] sexually active, noncontracepting women who had not conceived for 10 or more years were at a sixfold excess risk compared with other women. Whittemore and colleagues[237] similarly found a high risk associated with nulliparity despite unprotected intercourse, especially in women with long periods of ovulatory experience. Further exploration of the relationship of specific hormonal causes of infertility to ovarian cancer risk is warranted.

Menstrual Factors and Gynecologic Surgery

Most studies demonstrated no significant effect of age at menarche on the risk of ovarian cancer, although some indicated an increased risk associated with early menarche.[21,45,75,103,147,244] Numerous studies have noted a reduced risk of ovarian cancer associated with hysterectomy.[21,53,75,93,110,147,238] The apparent protective effect has ranged from 30% to 40%. Hysterectomy could appear to be protective simply because unilateral or bilateral oophorectomies were performed at the time of the hysterectomy, but studies that have validated interview information about removal of ovaries against medical records have shown that the protective effect persists for operations not involving the ovaries. The reduced risk associated with hysterectomy may reflect the opportunity for visualization and removal of abnormal ovaries during surgery. This interpretation is supported by data from Weiss and Harlow,[229] who found no reduced risk among women whose hysterectomies occurred more than 5 years before diagnosis. Another possibility is that a hysterectomy compromises ovarian function, possibly reducing blood supply to the ovaries.[67]

Late age at natural menopause has been related in some studies to a slightly increased risk of ovarian cancer.[21,244] It is uncertain why the effect seen is so weak compared with the marked flattening in the age-specific incidence curves shortly after menopausal ages.

Exogenous Hormones

Many studies have shown a reduced risk of ovarian cancer associated with the use of oral contraceptives. A reduction in risk is apparent after only a few months usage, but the apparent protection is greatest among long-term users.[21,43,45,188,231,240,244] In one study, the protective effect of long-term use ($\geq$10 years) reached 80%.[43] The reduction in risk appears to persist for a number of years after discontinuation[21,43,244] and applies to all histologic types of ovarian cancer.[43]

Most studies that have examined the effect of menopausal estrogens on ovarian cancer risk have not supported an association.[21,53,75,95,103,113,244] However, in one study, a threefold excess risk of endometrioid ovarian cancers was associated with any use of menopausal estrogens.[230] This was not supported in an additional study, although only a few exposed cases were involved.[112] Given the strong correlation of endometrial cancer risk with estrogen use, further evaluation of the effects of menopausal estrogens on the risk of endometrioid ovarian tumors appears warranted.

Dietary Factors

International data correlating ovarian cancer incidence and per capita fat availability and the increased incidence of ovarian cancer among Japanese migrants to the United States have stimulated interest in dietary factors.[8,86] There is some evidence that obesity may be a risk factor for ovarian cancer, possibly producing hyperestrogenism by peripheral conversion of androstenedione to estrone.[45] Follow-up studies provide some support for an association of ovarian cancer risk with fat intake, although the results are not consistent. A follow-up study of Seventh Day Adventists, many of whom are ovolactovegetarians, showed a standardized mortality ratio of ovarian cancer of about 0.6 compared with the general population.[177] Reporting the preliminary results of a 20-year follow-up study of 16,190 white Seven Day Adventists, Snowdon[211] found that women who consumed high amounts of eggs or fried food were at a threefold excess risk. It was suggested that the use of fat in the process of frying, especially animal fat, was more important than the intake of eggs.[185] However, Kinlen[118] found no reduction in ovarian cancer risk among nuns who completely or partially abstained from meat compared with other nulliparous women.

Case-control studies have also examined dietary factors. In one U.S. study, cancer patients consumed more whole milk, butter, animal fat, and saturated fat and less skimmed milk, margarine, vegetable fat, and unsaturated fat than controls.[55] Supporting these findings, La Vecchia and others[131] found significantly elevated risks among Italian women who reported frequent consumption of meat, ham, and fats, especially butter. In addition, low risks were associated with consumption of fish, green vegetables, carrots, and wholemeal bread or pasta. Shu and colleagues[201] reported a significant dose-response relationship between intake of fat from animal sources and risk of ovarian cancer in Chinese women, but they found no association with plant fat. Total vegetables were also associated with reduced risk. Slattery and others[207] found no effect from calories, fat, protein, fiber, or vitamins A and C, but a significant reduction in risk was associated with high consumption of β-carotene. Similarly, Byers and others[40] found no effect of fat, but they observed a protective effect from vitamin A intake among women between 30 and 49 years of age. These studies suggest that further attention should be focused on the role of dietary factors, particularly fats, carotenoids, and vitamins A and C.

Recently, Cramer and others[52] found a high risk of ovarian cancer associated with consumption of yogurt, cottage cheese, and other lactose-rich dairy products. This association was restricted to women with low levels of galactose-1-phosphate uridyl transferase activity, an enzyme linked with hypergonadotropic hypogonadism. These findings led to speculation that lactose consumption may be an environmental risk factor and transferase activity a genetic risk factor for ovarian cancer. Although further support for this hypothesis derives from a significant positive correlation between lactase persistence (i.e., ability to digest lactose after childhood) and ovarian cancer incidence in 27 countries, additional analytic studies are needed.[51]

Host Factors

Familial clusters of ovarian cancer suggest a genetic component. Several case-control studies have attempted to estimate the magnitude of the genetic contribution, with the largest of these studies showing relative risks of 3.6 and 2.9 associated with ovarian cancer in first- and second-degree relatives, respectively.[122,195]

Other Risk Factors

Interest in a possible etiologic role of talc exposure derives from the histologic similarity of ovarian cancer to mesothelioma and the chemical similarity of talc to asbestos, a known cause of mesothelioma. Four case-control studies reported an excess risk of ovarian cancer associated with perineal exposure to talc, although the lack of statistical significance of some of the findings and the absence of a relationship in most of these investigations with use of talc for diaphragm storage leads to questions about the biologic reality of the association.[56,89,92,238]

A history of mumps infection has been found to be a weak protective factor in several previous investigations, but the finding of a poor correlation between mumps serology and recall history has raised questions about the validity of exposure information.[157] Cramer and Welch[54] proposed that unapparent infections might result in oophoritis, oocyte depletion, and premature ovarian failure, leading to an excess risk of ovarian cancer. However, other studies failed to support this hypothesis.[194]

Smoking has not been related to ovarian cancer in most investigations, but some studies show slightly lower risks of ovarian cancer among alcohol drinkers.[40,77,85,95] Although it has been hypothesized that this may reflect the suppressive effects of alcohol on gonadotropin levels, other studies show no association between alcohol consumption and risk.[95,131] Coffee drinking, linked to an excess risk of ovarian cancer in several studies, has not been confirmed as a risk factor in other investigations.[94,133,159,219,238]

A recent report linked exposure to triazine herbicides to an elevated risk of ovarian cancer, an observation that requires further confirmation.[65]

TABLE 1–2.
Risk Factors for Ovarian Cancer

Factors Influencing Risk	Estimated Relative Risk*
Older ages	3
Residency in North America, Northern Europe	2–5
Higher levels of education or income	1.5–2
White race	1.5
Nulligravity	2–3
History of infertility	2–5
Early ages at menarche	1.5
Late ages at natural menopause	1.5–2
History of a hysterectomy	0.5–0.7
Use of oral contraceptives	0.3–0.5
Perineal talc exposure	1.5–2
Female relative with ovarian cancer	3–4

** Relative risks depend on the study and referent group employed.*

Carcinogenesis

Much of the clinical and epidemiologic evidence concerning risk factors for ovarian cancer implicates ovulatory activity. Conditions associated with reduced ovulation (e.g., pregnancy, oral contraceptive use, early menopause) are associated with reduced risk (Table 1-2). Even the weak evidence of reduced risk associated with lactation may be consistent with this synthesis, given the lack of correlation of duration of breastfeeding with extent of suppression of ovulation. Some investigators have been so persuaded by this potentially unifying hypothesis that they have amalgamated all the risk factors that protect against ovulation into a single index ("ovulatory age") and have found it to be a significant predictor of ovarian cancer risk.[45,75,103,183] However, in some instances this index, the period between menarche and menopause minus periods of pregnancy and oral contraceptive use, is less predictive of risk than the sum of its components assessed independently. This apparently results from variability in the effect of a year of ovulation inhibition, depending on the reason for such inhibition.

There are further questions about the mechanisms of protection associated with ovulatory inhibition or risks associated with "incessant ovulation." Three possible mechanisms have been postulated. An early suggestion based on the associations with parity and infertility was that there is some unidentified abnormality in endocrine function that may dispose women to relative or absolute infertility and ovarian cancer.[110] The protection associated with oral contraceptives seems unlikely to fit this hypothesis, unless, in some improbable manner, their use induces an endocrine milieu similar to that underlying fertility. A second popular unifying hypothesis is that ovarian cancer is the result of accumulated exposure to circulating pituitary gonadotropins.[54,212] Although this is consistent with the parity, menopause, and oral contraceptive associations, it does not explain the risks associated with clinical infertility, often associated with inadequate gonadotropin levels. Another inconsistency is the lack of protection associated with the use of hormone replacement therapy for the menopause, which also reduces gonadotropin levels. The third suggested explanation relates to the biologic impact of ovulation on the ovary. The cascade of epithelial events prompted by ovulation include minor trauma, a bathing of the surrounding tissue with estrogen-rich follicular fluid, and increased proliferation of epithelium, particularly near the point of ovulation, with resulting inclusions into the ovarian parenchyma. It has been suggested that some or all of these events may lie on the causal pathway to ovarian cancer.[71,247] This theory is consistent with most of the endocrine-related risk factors except for the risks associated with clinical infertility.

Although no one theory is currently accepted, there are possibilities for testing the proposed hypotheses. Discriminating between the roles of voluntary and involuntary infertility in producing the associations with parity would be useful. Characterizing the specific reproductive abnormalities that are responsible for the link between clinical infertility and ovarian cancer would be revealing. The possible relationship between increased galactose consumption and decreased galactose-1-phosphate uridyl transferase activity and subsequent increased risk of ovarian cancer noted in one study may operate through a mechanism of subclinical hypergonadatrophic hypogonadism. Attempts to replicate these findings could also contribute to elucidation of underlying mechanisms of carcinogenesis.

Attention to those associations not currently woven into one of the unifying hypotheses are warranted. Of particular interest is the consistently found but largely ignored finding of reduced ovarian cancer risk among those with prior uterine or fallopian tube surgery, predominantly hysterectomy and tubal ligation. Although initially thought to be an artifact of intraoperative screening, the accumulating evidence strongly argues against this. Attention to the effects of hysterectomy on the ovary and the hormonal milieu resulting from such surgery may yield important information about ovarian carcinogenesis.

With the current enthusiasm for the chemoprevention of cancer, the availability of drugs that modulate gonadotropin levels, and the specific nature of the gonadotropin-ovarian cancer hypothesis, particular attention should also be given to robust and timely opportunities to test this hypothesis.

CERVICAL CANCER

Demographic Patterns

An estimated 13,000 new cases of cervical cancer were diagnosed in the United States in 1991.[4] The average annual age-adjusted incidence in all SEER areas was 8.2 per 100,000 women for 1987, with a corresponding age-adjusted mortality rate for the years 1984 to 1987 of 3.1. The 5-year survival rate for cervical cancer is 67%, with the rate rising to 88% for cancers diagnosed at early stages.

Substantial decreases in the incidence of invasive cervical cancer have occurred over time in the United States (Fig. 1-5). Among whites, the incidence per 100,000 women declined 75% from 32.6 in the late 1940s to 8.3 in 1983 and 1984.[62] Mortality rates among whites declined markedly during the 1960s and 1970s. Average decreases in incidence and mortality have been about 4% per year. Although mortality and incidence rates have also declined among blacks, the decreasing mortality started later than among whites.

Throughout the period of declining incidence, the rates among blacks have remained about twice as high at all ages as among whites (Fig. 1-6). SEER data for 1987 indicate a twofold difference in age-adjusted incidence for invasive cervical cancer among blacks and whites. This differential, although previously observed for all ages, appears to be restricted now to older women. Among blacks the age-specific incidence of cervical cancer continues to rise, especially after 60 years of age, but among whites the rate plateaus after age 35, an unusual pattern of risk compared with other epithelial tumors. The incidence is also approximately two times higher for Hispanics and even higher for American Indians, but Asian groups experience rates similar to whites. Racial differences also exist in survival experience, with blacks having a 59% 5-year survival rate, compared with 67% among whites.

At least some of the racial differences can be explained by strong inverse associations observed between cervical cancer rates and socioeconomic indicators, such as education and income. These relationships prevail among both whites and blacks. When adjustment is made for socioeconomic differences, the excess risk of cervical cancer among blacks is substantially reduced from more than 70% to less than 30%.[60]

There are distinct geographic patterns in the United States, with high mortality rates scattered throughout the South, particularly in Appalachia (Fig. 1-7).[154] This reflects the tendency of the disease to affect rural women in lower socioeconomic classes.

There is tremendous geographic variation in the occurrence of invasive cervical cancer, with the highest rates reported from Latin America, where the risk is approximately six times that of U.S. whites, whose rates are among the lowest in the world. Even lower rates have been reported for Jewish women in Israel.[161]

Although recent upturns in incidence and mortality rates among young women have been observed in a number of countries, including Canada, Great Britain, New Zealand, and Australia, similar increases have not been seen in the United States, possibly because of the effectiveness of cytology screening programs, which may have counteracted anticipated increases from recent changes in risk factors.[63] The only evidence of increased incidence in the United States is for cervical adenocarcinomas among white women 35 to 54 years of age.[63]

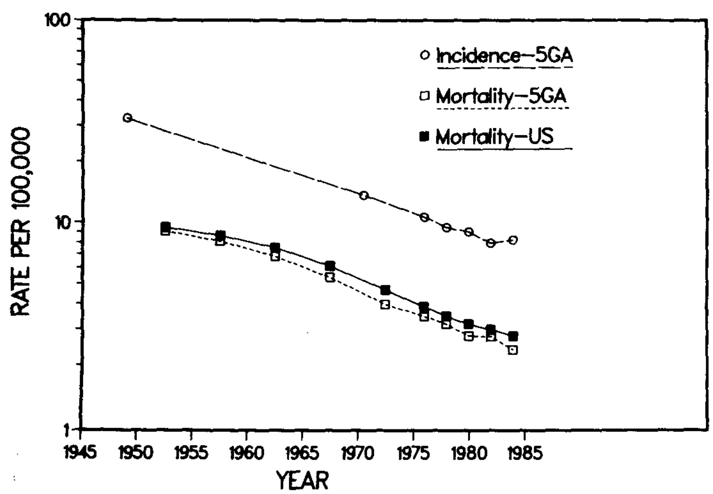

FIGURE 1–5. Incidence and mortality trends among U.S. white females for cancer of the cervix uteri. 5GA, five geographic areas. (Data from the Surveillance, Epidemiology, and End Results Program.)

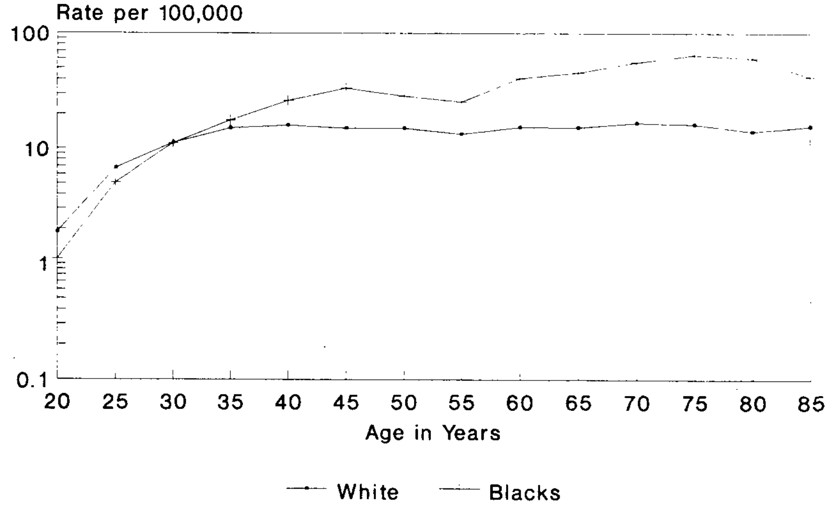

FIGURE 1–6. Age-specific incidence of invasive cancer of the cervix uteri by race. (Data from the Surveillance, Epidemiology, and End Results Program, 1987.)

Cytologic Screening

Cervical cancer is believed to result from the progression of milder epithelial abnormalities called dysplasia or cervical intraepithelial neoplasia. A new cytologic classification system, which combines clinically similar diagnoses into broad categories, including low-grade and high-grade squamous intraepithelial lesions, has also recently been proposed.[165] The gradient from the milder to more severe grades of neoplasia is characterized by increasing nuclear atypia and failure of cellular differentiation in progressively more superficial levels of epithelium, with carcinoma in situ representing full-thickness abnormality.

Support for a continuum of disease is provided by the observation that cervical dysplasia is most often diagnosed among women in their twenties, carcinoma in situ in women 30 to 39 years old, and invasive cancer after the age of 40. Although many dysplasias tend to spontaneously regress, particularly the milder grades, there is a definite tendency for progression over time. Thus, Stern and Neely[213] found that among women with cervical dysplasia, 48% were still dysplastic 1 to 7 years later, 40% had regressed to normalcy, 11% had progressed to carcinoma in situ, and 1% had progressed to invasive carcinoma. Hall and Walton,[87] in a 1- to 14-year follow-up study, reported a 29% progression rate to carcinoma in situ after severe dysplasia. In a 1- to 3-year study, Richart and Baron[182] found a progression rate of 20.3%. Peterson[176] observed a 33% progression rate from in situ disease to invasive carcinoma after 9 years among 127 women with untreated lesions.

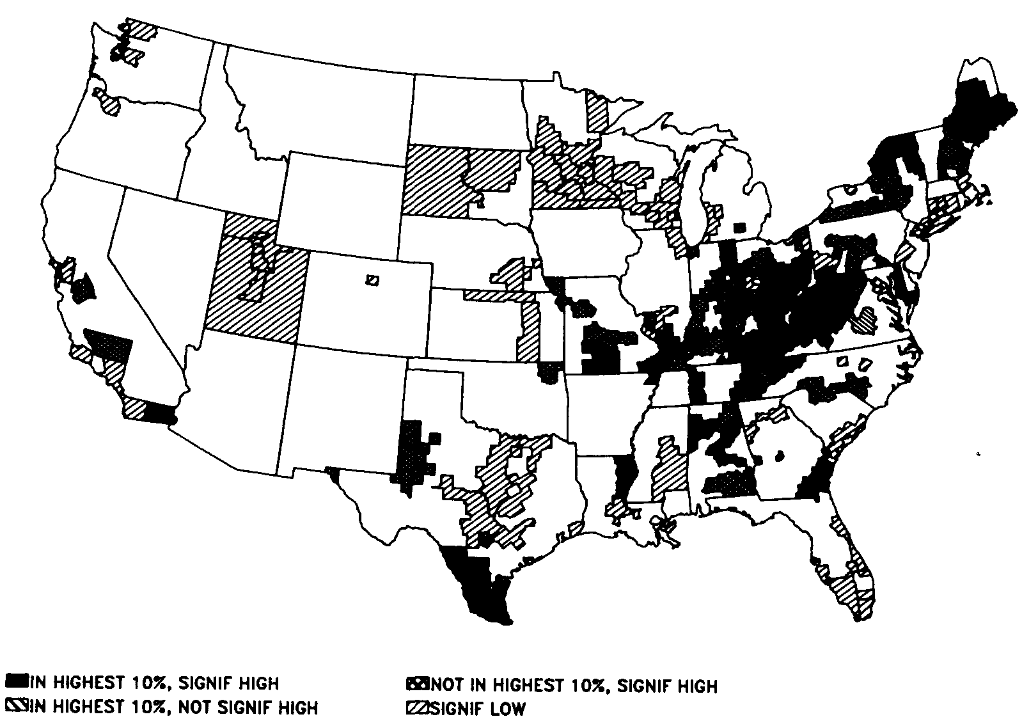

FIGURE 1–7. Cervical cancer mortality rates among U.S. white females by state economic area, 1970–1980.

The natural history of cervical lesions has been difficult to evaluate because of the curative effects of punch or cone biopsies used to diagnose dysplasias. To circumvent this disruption of the natural history, Kinlen and Spriggs[119] traced women without clinical evidence of cancer but with class 4 or 5 Papanicolaou (Pap) smears who did not return within 2 years for treatment. After a mean interval of 5.2 years, only 19 of 52 women had normal Pap smears or a biopsy that showed no lesion. Regression was confined to women younger than 40 at the time of the initial smear. In the remaining patients, dysplasia or carcinoma in situ was found in 20, microinvasive cancer in 3, and invasive carcinoma in 10.

Because of the presumed continuum of cervical disease from dysplasia to carcinoma in situ to invasive cancer, there is little doubt that exfoliative cytology or the Pap smear, a sensitive and inexpensive technique for detecting cervical cancer and its precursors, can have profound effects on morbidity and mortality. The eradication of precursor lesions has preceded significant declines in cervical cancer incidence and mortality in areas where screening has been widespread and prolonged, such as Kentucky and British Columbia.[23,47] The rates for cervical cancer have not declined in regions or countries with limited screening programs.[115] Case-control studies have evaluated the role of screening in preventing invasive cervical cancer. Clarke and Anderson[48] found a relative risk of 0.4 associated with screening within the last 5 years, and La Vecchia and others[134] found a relative risk of 0.2 if the patient had been screened within 3 to 5 years. In a Finnish study, even patients who had been screened more than 5 years previously had a relative risk of 0.7 compared with those who had never been screened.[169]

Sexual and Reproductive Factors

Early studies revealed that the risk of cervical cancer is especially high among single women and those marrying at young ages, but subsequent investigations targeted the risk to sexual behavior.[22,27,111,152,189,218] In a number of case-control studies, risk has been inversely related to age at first intercourse, with an approximately twofold differential between those with first intercourse before the age of 16 and after the age of 20, and directly related to lifetime number of sexual partners. Several studies have shown that the effect of age at first intercourse disappears after control for the number of sexual partners, although other studies have shown independent effects for both factors.[27,90,101,136,205] Most investigations have failed to find any influence on risk of the frequency of intercourse after accounting for the effects of other sexual risk factors.[22,27,111,152,189,218]

There is little evidence that age at menarche, age at menopause, or character of menses affect the risk of cervical cancer.[22,27,111,189] However, there is growing evidence to support an increased risk associated with multiple births.[27,33,171] In one study in Latin America, a fourfold greater risk of invasive cervical cancer was associated with 12 or more births than for one or fewer births, and the association persisted after adjustment for a variety of socioeconomic and sexual factors.[33] Possible explanations for the association include cervical trauma during parturition and hormonal or nutritional influences of pregnancy. Recent investigations showing high detection rates of human papillomaviruses (HPV) among pregnant women raise the possibility of viral influences.[197]

MALE PARTNER CONTRIBUTION

Despite extensive evidence implicating sexual factors in the cause of cervical cancer, there has been little attention given to the contribution of the male partner. Geographic clusters of cervical and penile cancers and elevated rates of cervical cancer among the wives of men with penile cancer first supported this idea.[44,76,79,153,210] A follow-up study showed that the wives of men previously married to cervical cancer patients had elevated rates of cervical neoplasia compared with control wives.[117] The most direct evidence for a male factor derives from studies in which the sexual histories of husbands of cervical cancer patients have been compared with those of control husbands.[34,37,250] In all of these studies, the husbands of cancer patients reported significantly more sexual partners than husbands of the controls. Buckley and others[37] observed that the husbands of affected women were also more likely to report prior venereal diseases, early sexual experiences, affairs during marriage, and visits to prostitutes. In contrast, there appears to be no effect on risk of circumcision status of the male partner, although this is notoriously difficult to evaluate epidemiologically.[22,34,111,189]

SEXUALLY TRANSMITTED AGENTS

The association of cervical neoplasia with sexual risk factors motivated the search for a venereally transmitted causative agent. Although the possible chemical carcinogenicity of semen and sperm has been suggested, most attention has focused on infectious agents, particularly herpes simplex virus type 2 (HSV-2) and HPV.[50]

Laboratory studies have demonstrated that HSV-2 infection can transform cells in culture and that HSV-2 proteins and integrated DNA can be found in some cervical cancers.[146] The epidemiologic evidence derives from serologic studies demonstrating higher prevalence of antibody to HSV-2 among patients with cervical neoplasia than among controls. This association has been documented in many geographic areas, using various assay methods. Investigations of invasive cancer have generally yielded higher risk estimates associated with HSV-2 antibodies than have studies of intraepithelial neoplasia.

Research interest in the oncogenic potential of HSV-2 declined after HSV-2 DNA and protein were not detected consistently in tumors and a large follow-up study of Czechoslovakian women failed to demonstrate a significantly increased risk of cervical neoplasia related to HSV-2 serology at enrollment.[225] However, the number of invasive cancers detected during this follow-up was small, limiting the statistical power of the findings. Although it is possible that the serologic evidence of elevated exposure to HSV-2 among cancer cases could represent an effect of disease or a noncausal association resulting from the correlation of HSV-2 with sexual activity, an etiologic role for HSV-2 has not been excluded. Nonetheless, most epidemiologic studies are now focused on HPV.[123]

Human papillomaviruses, double-stranded DNA viruses of approximately 8000 base pairs, form part of a family of papillomaviruses that include wart viruses of cattle, cotton-tailed rabbits, deer, and horses. There are more than 60 types of HPV known, with more identified each year. Types 1 and 2 cause deep plantar warts and common skin warts, respectively, and types 6 and 11 are the most common agents of venereal warts (condyloma acuminatum) and laryngeal polyps. Types 6, 11, 16, 18, 31, 33, 35, 39, 41 through 45, and 51 through 56 are known to infect genital epithelia, with types 6, 11, 16, and 18 being the most prevalent.[123]

Laboratory evidence for the oncogenic potential of HPV types is more compelling than the available epidemiologic data.[180] The similarity in microscopic appearance between mild dysplasia and HPV infection led to the discovery by electron microscopy and immunocytochemistry of HPV in neoplastic cervical tissues.[125] However, these techniques are relatively insensitive and, because serologic techniques are not generally available to permit an assessment of past exposure to relevant types of HPV, it was not until the application of DNA hybridization methods that the frequent presence of venereal HPV infection among cervical neoplasia patients was fully recognized. Most squamous cervical carcinomas and adenocarcinomas tested have been found to contain HPV, mainly types 16 and 18, and the same types are also found in cancer metastases.[127] Most preinvasive lesions also contain HPV, but the distribution of types is quite varied, suggesting that HPV type may be a factor differentiating low-risk from high-risk lesions.[126,141]

Only recently have analytic epidemiologic investigations been undertaken to estimate the relative risk of cervical neoplasia associated with HPV infection, with adjustment for known risk factors. One small study found no association between HPV 16 detection and risk of cervical cancer after adjustment for age.[155] However, a large investigation showed a relative risk of 9.1 associated with detection of high levels of HPV types 16 and 18 by filter in situ hybridization after controlling for the effects of age, sexual variables, parity, interval since last Pap smear, and education.[179]

Although the statistical association of HPV detection and cervical neoplasia appears firm, some contradictory epidemiologic data exist. In regional comparisons, reported HPV prevalence rates have not corresponded well with cervical cancer incidence.[1,121] The epidemiology of HPV infection has not been related in a convincing fashion to established sexual risk factors for cervical cancer, most notably the number of lifetime sexual partners.[179,223] Moreover, long-term prospective data on the carcinogenic risk of HPV infection are lacking. Only one small prospective study linking HPV presence and type to the progression of cervical intraepithelial neoplasia lesions has been reported.[41] Large follow-up studies of cytologically normal women, with HPV testing at enrollment, are now underway in several countries, but this will require years to yield reliable risk estimates.

Other infections may play independent or supporting etiologic roles.[2] Chlamydia has been suspected, based on case-control comparisons of serology and of chlamydia-associated changes seen on stored cervical smears.[3,192] Additional infections that have been studied include syphilis, gonorrhea, cytomegalovirus, Epstein-Barr virus, and bacterial vaginosis. No consistent association with cervical cancer risk has been observed for any of these agents. However, one investigation found an increased risk of cervical cancer with multiple, concurrent infections.[196] Most recently, infection with human immunodeficiency virus (HIV) has been correlated with the detection of HPV-related cytologic changes, and it is possible that the study of HIV-induced immunosuppression may clarify the interrelationships of cell-mediated immunity, HPV infection, and cervical neoplasia.[73]

Cigarette Smoking

In recent years, cigarette smoking has emerged as an important etiologic factor for cervical cancer.[242] Different types of epidemiologic investigations have demonstrated excess risks of both preinvasive and invasive cervical abnormalities among smokers. Although initially the relationship was thought to reflect the influence of correlated risk factors, such as sexual behavior, investigations that were able to control for a variety of extraneous factors found associations with smoking to persist.[31,49,132,206] In most studies, the excess risks for smokers have been around 2-fold, with the highest risks generally observed for long-term or high-intensity smokers. In several studies, the smoking relationship was restricted to current smokers, suggesting the possibility of a late-stage effect. Smoking effects appear to be restricted to squamous cell tumors, with no relationship observed for the rarer occurrences of adenocarcinoma or adenosquamous cancer.[31] Supporting a biologic mechanism for the smoking association are studies that have demonstrated high levels of smoke-derived nicotine and cotinine in the cervical mucus of smokers, although the immunosuppressive effects of smoking should also be considered, particularly in enhancing the effects of infectious agents, including HPV.[13,193]

Contraceptive Methods

Although initial studies examining the relationship of oral contraceptive use to cervical risk were reassuring, recent investigations have raised concern, particularly for long-term users. Issues of study design and analysis, however, are complex, generating questions about confounding factors, especially sexual behavior.[178] Even after considering correlated effects, most studies show some evidence of an increased risk, rising to approximately twofold for users of 5 or more years.[17,28,241] In several studies, higher risks have been observed for adenocarcinomas, in line with descriptive surveys showing increasing rates of this cell type among young women.[28,32,46,199]

In a number of studies, users of barrier methods of contraception have been shown to be at low risk of cervical cancer, presumably because of reduced exposure to infectious agents.[22,152,243] It has also been suggested that part of the protection associated with diaphragm use may reflect concurrent use of spermicides, which have antiviral properties.[102]

Dietary Factors

Risk of cervical cancer may be influenced by a variety of micronutrients. Two case-control studies, one in New York State and the other in Italy, suggested a protective effect of vegetables and fruits rich in carotenoids, with no apparent effect of animal foods containing preformed vitamin A, although both studies had rather limited dietary data.[128,151] Two U.S. case-control studies with more detailed dietary data have confirmed an association between dietary factors and cervical cancer risk, having found reduced risks associated with high dietary intake of carotenes, vitamin C, and vitamin E.[204,222] An Australian case-control study of carcinoma in situ, using a comprehensive food frequency interview and plasma measurements, found a strong protective effect of plasma β-carotene, but no independent association with either dietary vitamin A or carotenoids.[36] A similar inverse association with plasma β-carotene was reported in a British study, with the effect stronger for carcinoma in situ than for dysplasia.[91] The Australian study also showed reduced risk associated with dietary vitamin C intake, in agreement with two investigations in New York City. In one of these studies, vitamin C was measured through 3-day food records, and in the other, the effect was assessed by plasma measurements of vitamin C levels.[184,227] The most recent investigation, a large multicenter U.S. case-control study, found no association between risk and carotenoids, vitamin A, or vitamin C levels, as estimated through information on consumption of 75 food items.[248] Furthermore, risk was not affected by increased consumption of vegetables, dark green vegetables, dark yellow-orange vegetables, fruits, or legumes. Further investigations are needed to clarify the role of diet in the development of cervical cancer.

Folate deficiency has also been suggested as a cervical cancer risk factor on the basis of megaloblastic features in cervical cells of oral contraceptive users and findings that folate supplementation among oral contraceptive users with cervical dysplasia leads to marked cellular improvement.[39,236] However, epidemiologic studies employing dietary questionnaires have shown similar intakes of folate or folate-rich foods among women with invasive disease or in situ cervical cancer compared with controls.[36,248,249] The hypothesis deserves further attention, particularly with respect to a possible explanation for the effects of parity on cervical cancer. Pregnancy is associated with a depletion of maternal folate stores.

Host Factors

There is some suggestion that familial factors may play an etiologic role in cervical cancer.[115] Whether this tendency reflects environmental or genetic factors is unresolved. A further observation is that immunosuppression may play a role, because cervical cancer rates are elevated among immunosuppressed women, especially those with renal transplants, who are prone to a variety of genital infections, including HPV and HSV.[104,198] However, the excess cases have mainly involved in situ carcinomas, and their evaluation is complicated by close medical surveillance and difficulties in obtaining reliable expected values. Nonetheless, from animal studies there is reason to suspect that immunologic factors may be important, because infection with various HPV types (e.g., Shope papillomavirus in rabbits) is related to immune status. These viruses are antigenic, subject to immunologic destruction, and their occurrence is influenced by the immunologic competence of the host. An association has been reported between the presence of HPV types 16 and 18 and a reduction in Langerhans' cells, the local immunocompetent cells in the cervical epithelium. Thus, immunologic susceptibility should receive greater attention along with the role of HPV and other viruses.[198]

TABLE 1–3.
Risk Factors for Cervical Cancer

Factors Influencing Risk	Estimated Relative Risk*
Older ages	2
Residency in certain parts of Latin America, Asia or Africa	2–6
Lower levels of education or income	2–3
Black, Hispanic, or American Indian	2
Multiparity	2–4
Early ages at first sexual intercourse	2–4
Multiple sexual partners	2–5
Previous episodes of sexually transmitted diseases, especially genital herpes and warts	2–10
Long-term smoking	2–4
Long-term oral contraceptive use	1.5–2
No prior regular Pap smear screening	2–6
Diets low in carotene, vitamin C	2–3

**Relative risks depend on the study and referent group employed.*

Carcinogenesis

The consistent and dominant role of sexual factors in the etiology of cervical cancer has firmly implicated a venereally transmitted agent as the primary causal factor (Table 1-3). Because there is substantial evidence implicating HPV as these agents, most speculation over mechanisms of carcinogenesis revolve around the natural history of infection with these viruses. Most of what we know about these mechanisms derives from laboratory rather than epidemiologic evidence.

HPV has been shown to transform human cell lines in culture and to cause growth abnormalities that simulate early cervical intraepithelial neoplasia. HPV DNA, although found in an episomal (nonintegrated) form in early cervical lesions, is often found integrated into the cellular genome in cervical cancers and derived cancer cell lines; integration may therefore play a role in progression and maintenance of neoplasia. Protein products of HPV genes have been identified that interact with growth-regulator processes of the human cell, providing a possible mechanism for an HPV oncogenic effect.[123]

The potential for malignant transformation of papillomavirus-induced lesions has long been recognized. Cotton-tailed rabbit papillomavirus causes skin cancers in conjunction with exposure to coal tar, and bovine papillomavirus causes alimentary tract cancers in cows ingesting the cocarcinogen bracken fern. In the rare genetic disorder of epidermodysplasia verruciformis, patients develop multiple HPV-induced cutaneous warts that are prone to squamous cell carcinomas, especially in sun-exposed areas. Human venereal condylomas can similarly, although rarely, undergo malignant change.[124] In the cervix, the pathologic changes associated with HPV infection, called condylomatous or koilocytotic atypia, blend without clear distinction into the appearance of mild dysplasia.[156]

The complex natural history of cervical cancer imposes substantial difficulties on human investigations, including definition of disease; opportunity for bias in ascertainment of disease, which is linked to medical care, social class, and other risk factors; and the influence of screening and treatment for various precursor conditions. Additional difficulties are caused by the interrelationships among the risk factors for the disease. The high degree of correlation between number of sexual partners, age at first coitus, infection with various sexually transmitted diseases, use of oral contraceptives, cigarette smoking, socioeconomic status, nutrition, and screening practices conspire to confound our ability to identify independent risk factors.

Studies of the role of HPV in this process have been further complicated by substantial problems associated with the measurement of relevant exposures. Although it is clear that most biopsy specimens of cervical neoplasia contain HPV, it has proven difficult to determine the corresponding prevalence of HPV in women without cervical abnormalities. For them, only noninvasive cell sampling methods, such as swabs, scrapes, and lavages, are indicated, and the prevalence estimates may vary due to anatomic and quantitative differences in cell sampling.[221] Moreover, the presence or detectability of HPV among infected women, although poorly understood, is known with reasonable certainty to be intermittent, with single cross-sectional screenings underestimating HPV prevalence in controls and cases.[64] Regardless of cell sampling technique, the choice of DNA hybridization methods may strongly influence the results, and the various methods in common use have not been adequately standardized.[25,162] The true prevalence of HPV infection is still undefined, especially in normal women. Single cross-sectional estimates for cytologically normal women range from 1% to 35%, with repeated measurements or the use of ultrasensitive DNA detection techniques, such as the polymerase chain reaction (PCR), raising the estimates in certain studies to such a high level that the role of HPV as a sufficient cause of cancer of the cervix must be questioned.[14]

As more epidemiologists turn their energies to these problems and form interdisciplinary collaborations with clinical and laboratory researchers, information about papillomaviruses should clarify the relative roles of infection with various HPV types and the distinctions between exposure, latent infection, active infection, viral persistence and loss, and reinfection. These are probably the only types of studies that can also address the relationship of risk associated with HPV infection to those associated with other viruses, tobacco and other chemical carcinogens, hormones, and nutrients. Data on the likely multistage nature of HPV-associated neoplasia are vital to a complete understanding of cervical carcinogenesis and key to any attempts at primary prevention of this disease.

VULVAR CANCER

Demographic Patterns

Carcinoma of the vulva is a rare genital neoplasm, with an average annual age-adjusted incidence in all SEER areas during 1985 to 1987 of 1.5 per 100,000 women. Although vulvar cancer has been noted in clinical series to occur frequently in blacks, recent incidence data do not support any substantial differences in incidence by race. It occurs primarily in older women.

Cancers of the vulva occur significantly more frequently among women with primary cancers of the cervix, and the two diseases often occur simultaneously.[109,186] Approximately 15% to 20% of women with vulvar cancer have a second primary cancer occurring simultaneously or nonsimultaneously in the cervix, vagina, or anogenital area. A particularly high correlation exists between vulvar cancer and carcinoma of the cervix, and as many as 10% to 15% of women with cancer of the vulva have a second primary lesion of the cervix. If the multiple primaries are not diagnosed simultaneously, cancer of the cervix usually precedes cancer of the vulva. Many patients with vulvar cancer have multifocal genital lesions, commonly including a mixture of acuminatum condyloma planum and intraepithelial neoplasia. They may also have similar changes at other anogenital sites, including the vagina, cervix, and perianal region.[15,143]

It has been reported, however, that the incidence for carcinoma in situ of the vulva generally peaks at older ages, but the highest rates for in situ carcinoma of the cervix occur between 25 and 35 years of age. Invasive carcinomas of the vulva occur later than invasive carcinomas of the cervix, and the rates for invasive carcinomas of the vulva also do not increase as rapidly in the younger ages as the rates for carcinomas of the cervix. Using data from the Third National Cancer Survey, it was determined that 48% of the cases of invasive carcinoma of the cervix were diagnosed in women younger than 50 years of age, but only 15% of invasive vulvar cancers were diagnosed in women younger than 50 years of age.[97] These differences may reflect that the response of the cervix and vulva to the same carcinogenic stimulus varies with age and that the rate of response of the cervix is more rapid than that of response of the vulva. Furthermore, the vulva may be more responsive than the cervix to additional carcinogenic stimuli occurring at an older age.

Sexual, Social, and Reproductive Factors

A sexual cause has been postulated for vulvar carcinoma, with early studies showing serologic evidence of antibodies against HSV-2 in vulvar cancer patients and identification of HSV-2 in vulvar tumor tissue.[114] More recently, interest has focused on the role of HPV, because vulvar cancer is frequently associated with existing or preexisting condyloma acuminatum (genital warts), and malignant transformation of vulvar warts has been documented.[124,168] Vulvar carcinomas have been found to contain antigens and DNA from HPV. These findings suggest an infectious agent, but specific patterns of risk have not been pursued.

In one study, there appears to be a strong relationship between the number of sexual partners and observed risk, with women reporting five or more partners having two- to threefold greater risk than for those with one or fewer partners.[29] This factor largely explained crude associations of risk with early ages at first intercourse.

Although the incidence of vulvar cancer was believed to be inversely related to social class, results from one case-control study indicated that control for sexual factors eliminated this effect.[29] Suggestions that the risk of vulvar cancer is elevated among nulliparous women and those with late ages at first birth were also not confirmed in this study.

Medical Factors

Vulvar carcinomas often arise within genital warts, but more specific temporal associations between the two remain unclear. Several studies have suggested that a history of vulvar warts is associated with an elevated risk of vulvar cancer, with the relative excess risks ranging from 15- to 23-fold.[29,58] In one study, a particularly high risk was associated with multiple episodes of genital warts, possibly reflecting poor immunologic response among these women.[29]

Other Risk Factors

Several studies have shown an elevated risk of vulvar cancer associated with cigarette smoking.[29,142,166] In one study, elevations in risk were limited to current smokers, consistent with smoking acting as a late-stage carcinogen or promoter.[129] Smokers with a history of genital warts are at especially high risk, possibly supporting suggestions by zur Hausen[251] that the effects of HPV depend on the presence of cofactors. Given that smoking has been linked with immune alterations and that HPV is more common in immunosuppressed patients, further attention to the role of immune factors in vulvar cancer appears warranted.

Several clinical studies have suggested that vulvar cancer may be elevated among women with diabetes, obesity, or hypertension, but this has not been confirmed in the one epidemiologic study assessing these factors.[29] An excess risk of vulvar cancer among users of oral contraceptives was found in one study, but not in another.[29,166]

Carcinogenesis

The lack of extensive studies of this malignancy precludes any detailed discussion of the probable mechanisms of human carcinogenesis. The multicentric nature of the disease; its association with cervical, vaginal, and perianal malignancies; and several risk factors common to it and cervical cancer suggest that the etiologic mechanisms for vulvar and cervical cancer may be similar. The cervix and vulva are covered by a squamous cell epithelium with a common embryologic origin from the cloacogenic membrane. These similarities have led to the theory that the entire lower genital tract responds to various carcinogens as a single tissue field, resulting in a relatively high proportion of multicentric squamous carcinomas.[168]

VAGINAL CANCER

Demographic Patterns

Cancer of the vagina is rare, with an average annual age-adjusted incidence of 0.7 per 100,000 women in the SEER areas for the period from 1985 to 1987. The incidence is approximately three times higher for blacks than for whites, but the reasons for the discrepancy are unknown. About 1000 new cases and 350 deaths from vaginal cancer occur each year in the United States. The average 5-year survival rate is 46% for whites. Seventy-five percent of vaginal cancers are squamous cell carcinomas, and they usually occur in the upper part of the vagina.

Vaginal cancer is primarily a disease of older women, with almost 60% occurring among women 60 years or older. In the past, carcinoma of the vagina was only rarely reported in infants and children but, beginning in the late 1960s, cases of clear cell adenocarcinoma of the vagina, an uncommon cancer in any age group, began to be observed with much greater frequency than expected among women between 15 to 22 years of age. Most of these cases have been related to prenatal exposure to diethylstilbestrol (DES).

Risk Factors

Vaginal cancer occurs primarily among older women. Vaginal cancer has been reported to be rare in Jews, but no studies with proper control groups have tested this impression. Similarly, suggestions that the cancer correlates with marital status and parity are hard to interpret without appropriate comparison groups.[115]

Few etiologic studies of this cancer have been conducted, and most clues for this cancer derive from clinical studies. Among factors that have been suggested, trauma to the vagina has received the most attention. Injury to the vagina from wearing ring pessaries (i.e., to support the uterus or rectum or as a contraceptive device) has been mentioned as a possible cause of vaginal carcinoma.[191] Other suggested agents are chronic leukorrhea, leukoplakia, chronic vaginitis, intercourse, trauma from childbirth, late menopause, masturbation, heavy body build, exposure to chemicals in the vagina, douching, and viruses.[115] The one case-control study of vaginal cancer, based on relatively few cases ($n=41$), found associations of risk with low socioeconomic status, histories of genital warts or other genital irritations, and previous abnormal Pap smears.[30] Women who had previous hysterectomies were at high risk, consistent with several clinical observations, but in contrast to one analytic study, in which cases with vaginal cancer were matched with controls on history of previous dysplasia or neoplasia of the cervix.[16,100,216]

Vaginal cancer is frequently found as a synchronous or a metachronous neoplasm with cervical cancer.[186] This has led to the suggestion that there may be shared etiologic features between vaginal and cervical cancers. There have been reports of the coexistence of condylomatous lesions with vaginal cancer and the existence of human papillomavirus antigens or DNA in vaginal cancer tissue.[168]

Diethylstilbestrol and Clear Cell Adenocarcinomas

In 1971, 7 patients with clear cell carcinoma of the vagina and 1 patient with the closely related endometrioid carcinoma were reported from Boston among women whose ages ranged from 15 to 22 years.[99] The mothers of 7 of the 8 women had taken DES during the first trimester of pregnancy. None of the mothers of 32 matched controls had taken DES. The relationship between DES exposure in utero and adenocarcinoma of the vagina was soon confirmed in New York State, and a similar association was observed at the Mayo Clinic.[82,167] Since then, a registry of clear cell cancer of the vagina and cervix has been established, and many more cases have been reported.[98] Among these patients, about twice as many have clear cell adenocarcinoma of the vagina as have clear cell adenocarcinoma of the cervix.

Data from the Adenocarcinoma Registry revealed that approximately 65% of the patients had documented prenatal exposure to DES or to the chemically related compounds dienestrol or hexestrol. Most patients are diagnosed between 14 and 23 years of age, with a peak at 19 years. This relatively narrow age range suggests that, in addition to DES exposure, some factors associated with the onset of puberty are necessary for the development of the cancer. It is not yet known whether cases will occur at later ages as the exposed cohort becomes older. It has been estimated that the risk of developing clear cell adenocarcinoma of the vagina and cervix before 24 years of age is between 0.14 and 1.4 per 1000 DES-exposed daughters.

In all but one of the Registry cases, the treatment had begun before the 18th week of gestation, with the relative risk being highest for those whose mothers began DES before the 12th week of pregnancy. In addition, higher risks were observed for DES daughters born in the fall (winter conceptions). Maternal history of at least one prior spontaneous abortion was also linked with high risk, raising the possibility that an inherited genetic predisposing factor may play a role in some cases.

Carcinogenesis

Even less is known about risk factors for the form of vaginal cancer in the elderly than is known for vulvar cancer, making any discussion of mechanisms of carcinogenesis totally speculative. However, it appears from limited data that further attention should focus on the role of sexually transmitted agents, specifically the human papillomaviruses.

The rare occurrence of vaginal adenocarcinoma in young women is essentially an iatrogenic disease related to in utero exposure to DES and other estrogens. Specific suggested mechanisms of carcinogenesis focus on the retention of nests of abnormal cells of müllerian duct origin, which after stimulation by endogenous hormones during puberty are promoted into adenocarcinomas.

MALIGNANT TROPHOBLASTIC DISEASE

Demographic Patterns

Choriocarcinoma is a rare malignancy in the United States, with a recent incidence in all SEER areas of 0.2 per 100,000 women, or approximately 1 per 22,623 live births.[26] Hydatidiform mole occurs about once in every 1000 pregnancies, and approximately 1 of 6 occurrences results in invasive complications. Trophoblastic diseases have been reported to be more common in certain parts of the world, although part of the differences may be due to a variety of selection biases.[24] The epidemiologic study of choriocarcinoma has been complicated by its relative infrequency. Most studies have therefore focused on defining risk factors for hydatidiform or invasive mole, and it is uncertain the extent to which these findings can be extrapolated to malignant trophoblastic disease, including invasive hydatidiform mole and choriocarcinoma.

Host Factors

Apart from a history of hydatidiform mole, the most clearly established risk factor for choriocarcinoma and for hydatidiform mole is late maternal age. A Singapore study observed a 24-fold increased incidence for women older than 45, compared with those between 20 and 39 years; this incidence among older women translated into a rate of one case of choriocarcinoma for every 185 live births.[217]

There also appear to be racial differences in the incidence of malignant trophoblastic disease. Rates appear to be considerably higher in Asian and African countries, but the true extent of difference from Western rates is difficult to decipher because of variations in reporting practices. One incidence survey in the United States showed that, even after adjustment for age and birth distribution effects, blacks had a 2.1-fold greater risk and other nonwhite races had a 1.8-fold greater risk than whites.[26]

An association between blood group A and choriocarcinoma has been found in two studies, and the combination of mother's group A and father's group O was considerably higher than expected (10.4-fold risk).[10,11,59] Blood groups A and AB were associated with elevated risks of hydatidiform mole in one study, although blood group was not predictive of risk in two others.[158,170,217] These findings may support a role for genetic factors or immunologic factors related to the histocompatibility of maternal and trophoblastic tissues.

Menstrual and Reproductive Factors

In several studies that have adjusted for the effects of late maternal age, parous women have remained at a substantially reduced risk of hydatidiform mole compared with nulliparous women, with some evidence of further reductions in risk with multiple births.[35,158,172] Several studies found an increased risk associated with the occurrence of a prior spontaneous abortion, although this was not consistently observed.[35,137,158,172] An increased risk of hydatidiform mole was associated with induced abortions, although information was not available on reasons for the terminations.[35] A history of infertility has also been suggested as a risk factor for gestational trophoblastic disease, although not confirmed in all studies.[35,137,158] In one study, Chinese patients reporting use of herbal medicines during the first trimester of a previous pregnancy were at elevated risk.[35] This is of interest because laboratory findings indicate that choriocarcinoma can be induced in monkeys by exposure to ethylnitrosourea.[181]

Low body mass index, unrelated to dieting or exercise, has been reported as a risk factor for choriocarcinoma in one study.[38] Patients also had later onset of menarche and lighter menstrual periods than controls, possibly reflecting lower estrogen levels.

Exogenous Hormones

Several studies have found an increased risk of trophoblastic diseases associated with long-term use of oral contraceptives.[18,35,187] Two other case-control studies, however, found no influence of oral contraceptives on risk.[137,158] Others have suggested that oral contraceptives may increase the risk of malignant sequelae after mole evacuation through a tumor-stimulating effect.[215,246] In one study, this effect was restricted to users of high-dose estrogens, although in others, there were no effects of the pill on postmolar complications.[18,57,160,246]

Other Risk Factors

Late paternal age was suggested to increase the risk of trophoblastic diseases, but other investigations failed to confirm this.[35,138,158] Cigarette smoking has also been linked with the occurrence of trophoblastic disease.[137] One study suggested that low carotene intake affected the risk of hydatidiform mole, but no specific dietary associations were observed in another study.[18,35]

Carcinogenesis

Although a genetic role in the development of hydatidiform mole is now certain, almost nothing is known about genotypes that are precursors to hydatidiform mole or environmental factors that may increase the risk of defective ova. Except for the possible role of oral contraceptives, we are also ignorant of environmental factors that may act as promoters of choriocarcinoma after hydatidiform mole.

The trophoblast plays an active role in pregnancy, including metabolizing and detoxifying xenobiotic substances, regulating nutrient and waste product transfer, synthesizing steroid and protein hormones, and controlling the immune response of the maternofetal unit. Injury to the trophoblast can occur in pregnancy as a result of environmental exposure (e.g., heavy metals and polycyclic hydrocarbons), resulting in the breakdown of trophoblastic processes. When the trophoblast malfunctions, mutagenic, teratogenic, fetotoxic, and carcinogenic compounds gain access to the developing embryo, causing injury and death. The genotype of hydatidiform mole results in a trophoblast that malfunctions, and exposure to certain environmental agents during the molar pregnancy may promote choriocarcinoma. Before implantation, the trophoblast forms most of the embryonic tissue, which already metabolizes environmental agents. Even preimplanted moles, with their impaired metabolic capabilities, may increase the toxicity of environmental agents and promote carcinogenesis.

COMMENTARY

The goal of medical practice is the reduction of morbidity and mortality. For many diseases, the focus has turned to the ultimate aim of prevention. Unfortunately, this has rarely been possible for malignancy, and the practitioner of oncology has been forced to deal with measures that prevent or delay mortality and those that minimize cancer-related morbidity. Discussion of these measures occupies almost all of this text. More attention cannot be given to primary prevention because of the paucity of knowledge about the causes of most malignancies. A correlation between identification of etiologic factors and possibilities for prevention is reasonable and well illustrated for tobacco- and alcohol-related tumors and for those associated with radiation, occupational, and specific drug exposures.

If there is a strong link between etiology and prospects for prevention, gynecologic cancers are the category of malignancies most amenable to preventive approaches. Prospects are perhaps best for cervical cancer. For some time, secondary prevention in the form of screening for pathologic precursors of invasive disease has been the hallmark of the public health approach to this malignancy. Preventive action, focused first on carcinoma in situ and then on the more severe forms of dysplasia, have been associated with marked declines in mortality. If a central role for type-specific HPV infection modified by a variety of cofactors proves to be the correct model for this disease, many preventive opportunities should follow.

Knowledge of when and how infection and other factors operate in the natural history of the disease could revolutionize screening strategies. The form of treatment could also be revolutionized from ablation of cells to antiviral therapies. Moreover, investigators are actively pursuing the development of vaccines. Basic laboratory, clinical, and epidemiologic research is needed to effect any of these propositions.

Many believe that more is known about the cause of endometrial carcinoma than for almost any other tumor. A unified theory of how all risk factors may operate through a final common estrogenic pathway is popular and well supported. Although interesting to those studying carcinogenesis, is a woman's hormonal milieu subject to favorable modification at a practical level? Perhaps more so than is realized. There is substantial evidence that elimination of obesity and a reduction in fat in the diet, two interventions actively promoted for other reasons, should also reduce endometrial cancer risk. After the epidemic of endometrial cancer due to estrogen replacement therapy, changes in management of menopause occurred, resulting in a marked decline in the rates of endometrial cancer. More care is devoted to identifying women who truly need estrogen therapy; treatment of menopausal symptoms is for a much shorter period of time; use of cyclic progestin in combination with estrogen is advised if indicated; and regular endometrial sampling is frequently practiced for long-term estrogen users.

Although past alterations in patient management led to a decline in endometrial cancer, current events make future patterns less clear. There is growing enthusiasm for long-term treatment of large segments of the population of menopausal women with hormones to prevent osteoporosis and heart disease. If this trend continues, much more attention must be given to controlling endometrial cancer risk. On the other hand, current patterns of use of oral contraceptives could lead to reductions in endometrial cancer rates in the general population. The impact of widespread oral contraceptive use by young women on their endometrial cancer risk when they reach the high-risk age group for this tumor is not well studied. However, if it is anywhere near the reduced risk seen at young ages, the resulting reduction in endometrial cancer overall could be substantial.

With further research, it is also possible that pharmacologic interventions aimed specifically at groups with high risk of endometrial cancer due to endogenous normal factors could be justified. More must be learned about the associations of risk for endometrial cancer and the quantitative levels of estrogens and other hormones and their relative proportions. Once these factors are known, it is possible that women with polycystic ovarian disease, diabetes, morbid obesity, or other predisposing conditions could be evaluated and that those with substantially unfavorable hormone profiles could be appropriately treated.

Although a substantial amount has been learned about ovarian cancer risks, the prospects for meaningful preventive measures aimed at this tumor are probably worse than for the other gynecologic malignancies. Although several ovarian cancer factors seem to indict ovulatory activity as a common pathway to increased risk, the mechanism by which this occurs is unknown. Even if some of the hypothesized mechanisms prove correct (e.g., levels of circulating gonadotrophins), it is unclear how reasonable any interventions may be. However, if the long-term effect of oral contraceptive use on ovarian cancer risk is similar to its short-term effect, a substantial decline in ovarian cancer rates should result from pill use patterns of the past 30 years. Another reason for the limited prospects for prevention is that for several risk factors (e.g., protection associated with hysterectomy), no credible mechanism has been suggested. The associations promising the greatest opportunities for preventive actions are the recently suggested dietary relationships, specifically increased risk with high-fat diets and lactose consumption, particularly in individuals whose metabolism could lead to lactose persistence. However, these observations have yet to be replicated in convincing studies. Because of the preventive implications, attempts at confirmation should have high priority.

For cervical cancer, endometrial cancer, and ovarian cancer, much is known about risk factors. The research gaps that do exist are in defining the precise biologic mechanisms through which the known risk factors operate. There is substantial enthusiasm for current interdisciplinary studies that incorporate state-of-the-art laboratory assays into robust epidemiologic research designs focused on answering these mechanistic questions. Even among some of the more conservative etiologists, there is a belief that the gynecologic oncologist may soon be able to intervene much earlier in the natural history of these diseases, and in some instances, engage in primary prevention.

REFERENCES

1. Acs J, Hildesheim A, Reeves WC, et al: Regional distribution of human papillomavirus DNA and other risk factors for invasive cervical cancer in Panama. Cancer Res 49:5725, 1989.
2. Alexander ER: Possible etiologies of cancer of the cervix other than herpesvirus. Cancer Res 33:1485, 1973.
3. Allerding TJ, Jordan SW, Boardman RE: Association of human papillomavirus and chlamydia infections with incidence cervical neoplasia. Acta Cytol 29:653, 1985.
4. American Cancer Society: Cancer Statistics 1991. CA 41:1, 1991.
5. Antunes CMF, Stolley PD, Rosenshein NB, et al: Endometrial cancer and estrogen use. Report of a large case-control study. N Engl J Med 300:9, 1979.
6. Armstrong BK: Diet and hormones in the epidemiology of breast and endometrial cancers. Nutr Cancer 1:90, 1979.
7. Armstrong BK, Brown JB, Clarke HT, et al: Diet and reproductive hormones: A study of vegetarian and nonvegetarian postmenopausal women. JNCI 67:761, 1981.
8. Armstrong B, Doll R: Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. Int J Cancer 15:617, 1975.
9. Austin H, Austin JM Jr, Partridge EE, et al: Endometrial cancer, obesity, and body fat distribution. Cancer Res 51:568, 1991.
10. Bagshawe KD: Risk and prognostic factors in trophoblastic neoplasia. Cancer 38:1373, 1976.
11. Bagshawe KD, Rawlins G, Pike MC, et al: ABO blood groups in trophoblastic neoplasia. Lancet 1:553, 1971.
12. Baron JA, Byers T, Greenberg ER, et al: Cigarette smoking in women with cancers of the breast and reproductive organs. JNCI 77:677, 1986.
13. Barton SE, Jenkins D, Cuzick J, et al: Effect of cigarette smoking on cervical epithelial immunity: A mechanism for neoplastic change? Lancet 2:652, 1988.
14. Bauer HM, Ting Y, Greer CE, et al: Genital human papillomavirus infection in female university students as determined by a PCR-based method. JAMA 265:472, 1991.
15. Beckmann AM, Kiviat NB, Daling JR, et al: Human papillomavirus type 16 in multifocal neoplasia of the female genital tract. Int J Gynecol Pathol 7:39, 1988.
16. Bell J, Sevin B, Averette H, et al: Vaginal cancer after hysterectomy for benign disease: Value of cytologic screening. Obstet Gynecol 54:699, 1984.
17. Beral V, Hannaford P, Kay C: Oral contraceptive use and malignancies of the genital tract. Results from the Royal College of General Practitioners' Oral Contraception Study. Lancet 2:1331, 1988.
18. Berkowitz RS, Cramer DW, Bernstein MR, et al: Risk factors for complete molar pregnancy from a case-control study. Am J Obstet Gynecol 152:1016, 1985.
19. Bernstein L, Pike MC, Ross RK, et al: Estrogen and sex hormone-binding globulin levels in nulliparous and parous women. JNCI 74:741, 1985.
20. Blitzer PH, Blitzer EC, Rimm AA: Association between teen-age obesity and cancer in 56,111 women: All cancers and endometrial carcinoma. Prev Med 5:20, 1976.
21. Booth M, Beral V, Smith P: Risk factors for ovarian cancer: A case-control study. Br J Cancer 60:592, 1989.
22. Boyd JT, Doll R: A study of the aetiology of carcinoma of the cervix uteri. Br J Cancer 18:419, 1964.
23. Boyes DA: The value of a Pap smear program and suggestions for its implementation. Cancer 48:613, 1981.
24. Bracken MB, Brinton LA, Hayashi K: Epidemiology of hydatidiform mole and choriocarcinoma. Epidemiol Rev 6:52, 1984.
25. Brandsma J, Burk RD, Lancaster WD, et al: Inter-laboratory variation as an explanation for varying prevalence estimates of human papillomavirus infection. Int J Cancer 43:260, 1989.
26. Brinton LA, Bracken MB, Connelly RR: Choriocarcinoma incidence in the United States. Am J Epidemiol 123:1094, 1986.
27. Brinton LA, Hamman RF, Huggins GR, et al: Sexual and reproductive risk factors for invasive squamous cell cervical cancer. JNCI 79:23, 1987.
28. Brinton LA, Huggins GR, Lehman HF, et al: Long-term use of oral contraceptives and risk of invasive cervical cancer. Int J Cancer 38:339, 1986.
29. Brinton LA, Nasca PC, Mallin K, et al: Case-control study of cancer of the vulva. Obstet Gynecol 75:859, 1990.
30. Brinton LA, Nasca PC, Mallin K, et al: Case-control study of in situ and invasive carcinoma of the vagina. Gynecol Oncol 38:49, 1990.
31. Brinton LA, Schairer C, Haenszel W, et al: Cigarette smoking and invasive cervical cancer. JAMA 255:3265, 1986.
32. Brinton LA, Reeves WC, Brenes MM, et al: Oral contraceptive use and risk of invasive cervical cancer. Int J Epidemiol 19:4, 1990.
33. Brinton LA, Reeves WC, Brenes MM, et al: Parity as a risk factor for cervical cancer. Am J Epidemiol 130:486, 1989.
34. Brinton LA, Reeves WC, Brenes MM, et al: The male factor in the etiology of cervical cancer among sexually monogamous women. Int J Cancer 44:199, 1989.
35. Brinton LA, Wu B, Wang W, et al: Gestational trophoblastic disease: A case-control study from the People's Republic of China. Am J Obstet Gynecol 161:121, 1989.
36. Brock KE, Berry G, Mock PA, et al: Nutrients in diet and plasma and risk of in situ cervical cancer. JNCI 80:580, 1988.
37. Buckley JD, Harris RWC, Doll R, et al: Case-control study of the husbands of women with dysplasia or carcinoma of the cervix uteri. Lancet 2:1010, 1981.
38. Buckley JD, Henderson BE, Morrow CP, et al: Case-control study of gestational choriocarcinoma. Cancer Res 48:1004, 1988.
39. Butterworth CE Jr, Hatch KD, Gore H, et al: Improvement in cervical dysplasia associated with folic acid therapy in users of oral contraceptives. Am J Clin Nutr 35:73, 1982.
40. Byers T, Marshall J, Graham S, et al: A case-control study of dietary and nondietary factors in ovarian cancer. JNCI 71:681, 1983.
41. Campion MJ, McCance DJ, Cuzick J, et al: Progressive potential of mild cervical atypia: Prospective cytological, colposcopic, and virological study. Lancet 2:237, 1986.
42. Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development: Combination oral contraceptive use and the risk of endometrial cancer. JAMA 257:796, 1987.
43. Cancer and Steroid Hormone Study of the Centers for Disease

Control and the National Institute of Child Health and Human Development: The reduction in risk of ovarian cancer associated with oral-contraceptive use. N Engl J Med 316:650, 1987.

44. Cartwright RA, Sinson JD: Carcinoma of penis and cervix. Lancet 1:97, 1980.
45. Casagrande JT, Pike MC, Ross RK, et al: "Incessant ovulation" and ovarian cancer. Lancet 2:170, 1979.
46. Chilvers C, Mant D, Pike MC: Cervical adenocarcinoma and oral contraceptives, Br Med J 295:1446, 1987.
47. Christopherson WM, Parker JE, Mendez WM, et al: Cervix cancer death rates and mass cytologic screening. Cancer 26:808, 1970.
48. Clarke EA, Anderson TW: Does screening by "Pap" smears help prevent cervical cancer? A case-control study. Lancet 2:1, 1979.
49. Clarke EA, Morgan RW, Newman AM: Smoking as a risk factor in cancer of the cervix: Additional evidence from a case-control study. Am J Epidemiol 115:59, 1982.
50. Coppleson M: The origin and nature of premalignant lesions of the cervix uteri. Int J Gynaecol Obstet 8:539, 1970.
51. Cramer DW: Lactase persistence and milk consumption as determinants of ovarian cancer risk. Am J Epidemiol 130:904, 1989.
52. Cramer DW, Harlow BL, Willett WC, et al: Galactose consumption and metabolism in relation to the risk of ovarian cancer. Lancet 2:66, 1989.
53. Cramer DW, Hutchison GB, Welch WR, et al: Determinants of ovarian cancer risk. I. Reproductive experiences and family history. JNCI 71:711, 1983.
54. Cramer DW, Welch WR: Determinants of ovarian cancer risk. II. Inferences regarding pathogenesis. JNCI 71:717, 1983.
55. Cramer DW, Welch WR, Hutchison GB, et al: Dietary animal fat in relation to ovarian cancer risk. Obstet Gynecol 63:833, 1984.
56. Cramer DW, Welch WR, Scully RE, et al: Ovarian cancer and talc. A case-control study. Cancer 50:372, 1982.
57. Curry SL, Schlaerth JB, Kohorn EI, et al: Hormonal contraception and trophoblastic sequelae after hydatidiform mole (a Gynecologic Oncology Group study). Am J Obstet Gynecol 160:805, 1989.
58. Daling JR, Chu J, Weiss NS, et al: The association of condylomata acuminata and squamous carcinoma of the vulva. Br J Cancer 50:533, 1984.
59. Dawood MY, Teoh ES, Ratnam SS: ABO blood group in trophoblastic disease. J Obstet Gynaecol Br Commonw 78:918, 1971.
60. Devesa SS, Diamond EL: Association of breast cancer and cervical cancer incidences with income and education among whites and blacks. JNCI 65:515, 1980.
61. Devesa SS, Silverman DT: Cancer incidence and mortality trends in the United States: 1935–74. JNCI 60:545, 1978.
62. Devesa SS, Silverman DT, Young JL Jr, et al: Cancer incidence and mortality trends among whites in the United States, 1947–84. JNCI 79:701, 1987.
63. Devesa SS, Young JL Jr, Brinton LA, et al: Recent trends in cervix uteri cancer. Cancer 64:2184, 1989.
64. de Villiers EM, Wagner D, Schneider A: Human papillomavirus infections in women with and without abnormal cervical cytology. Lancet 2:703, 1987.
65. Donna A, Crosignani P, Robutti F, et al: Triazine herbicides and ovarian epithelial neoplasms. Scand J Work Environ Health 15:47, 1989.
66. Elliott EA, Matanokis GM, Rosenshein NB, et al: Body fat patterning in women with endometrial cancer. Gynecol Oncol 39:253, 1990.
67. Ellsworth LR, Allen HH, Nisker JA: Ovarian function after radical hysterectomy for stage 1B carcinoma of the cervix. Am J Obstet Gynecol 145:185, 1983.
68. Elwood JM, Boyes DA: Clinical and pathological features and survival of endometrial cancer patients in relation to prior use of estrogens. Gynecol Oncol 10:173, 1980.
69. Elwood JM, Cole P, Rothman KJ, et al: Epidemiology of endometrial cancer. JNCI 59:1055, 1977.
70. Farhi DC, Nosanchuk J, Silverberg SG: Endometrial adenocarcinoma in women under 25 years of age. Obstet Gynecol 61:966, 1986.
71. Fathalla MF: Incessant ovulation—a factor in ovarian neoplasia? Lancet 2:163, 1971.
72. Fechner RE, Kaufman RH: Endometrial adenocarcinoma in Stein-Leventhal syndrome. Cancer 34:444, 1974.
73. Feingold AR, Vermund SH, Burk RD, et al: Cervical cytologic abnormalities and papillomavirus in women infected with human immunodeficiency virus. J Acquir Immune Defic Syndr 3:896, 1990.
74. Folsom AR, Kaye SA, Potter JD, et al: Association of incident carcinoma of the endometrium with body weight and fat distribution in older women: Early findings of the Iowa Women's Health Study. Cancer Res 49:6828, 1989.
75. Franceschi S, La Vecchia C, Helmrich SP, et al: Risk factors for epithelial ovarian cancer in Italy. Am J Epidemiol 115:714, 1982.
76. Franco EL, Filho NC, Villa LL, et al: Correlation patterns of cancer relative frequencies with some socioeconomic and demographic indicators in Brazil: An ecologic study. Int J Cancer 41:24, 1988.
77. Franks AL, Lee NC, Kendrick JS, et al: Cigarette smoking and the risk of epithelial ovarian cancer. Am J Epidemiol 126:112, 1987.
78. Gambrell RD Jr, Bagnell CA, Greenblatt RB: Role of estrogens and progesterone in the etiology and prevention of endometrial cancer: Review. Am J Obstet Gynecol 146:696, 1983.
79. Graham S, Prior R, Graham M, et al: Genital cancer in wives of penile cancer patients. Cancer 44:1870, 1979.
80. Gray LA, Christopherson WM, Hoover RN: Estrogens and endometrial carcinoma. Obstet Gynecol 49:385, 1977.
81. Greenblatt RB, Gambrell RD Jr, Stoddard LD: The protective role of progesterone in the prevention of endometrial cancer. Pathol Res Pract 174:297, 1982.
82. Greenwald P, Barlow JJ, Nasca PC, et al: Vaginal cancer after maternal treatment with synthetic hormones. N Engl J Med 285:390, 1974.
83. Gusberg SB: The changing nature of endometrial cancer. N Engl J Med 302:729, 1980.
84. Gusberg SB, Kardon P: Proliferative endometrial response to thecagranulosa cell tumors. Am J Obstet Gynecol 111:633, 1971.
85. Gwinn ML, Webster LA, Lee NC, et al: Alcohol consumption and ovarian cancer risk. Am J Epidemiol 123:759, 1986.
86. Haenszel W, Kurihara M: Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. JNCI 40:43, 1968.
87. Hall JE, Walton L: Dysplasia of the cervix: A prospective study of 206 cases. Am J Obstet Gynecol 100:662, 1968.
88. Hammond CB, Jelovsek FR, Lee KL, et al: Effects of long-term estrogen replacement therapy. II. Neoplasia. Am J Obstet Gynecol 133:537, 1979.
89. Harlow BL, Weiss NS: A case-control study of borderline ovarian tumors: The influence of perineal exposure to talc. Am J Epidemiol 130:390, 1989.
90. Harris RWC, Brinton LA, Cowdell RH, et al: Characteristics of women with dysplasia or carcinoma in situ of the cervix uteri. Br J Cancer 42:359, 1980.
91. Harris RWC, Forman D, Doll R, et al: Cancer of the cervix uteri and vitamin A. Br J Cancer 53:653, 1986.
92. Hartge P, Hoover R, Lesher LP, et al: Talc and ovarian cancer [letter]. JAMA 250:1844, 1983.
93. Hartge P, Hoover R, McGowan L, et al: Menopause and ovarian cancer. Am J Epidemiol 127:990, 1988.
94. Hartge P, Lesher LP, McGowan L, et al: Coffee and ovarian cancer [letter]. Int J Cancer 30:531, 1982.
95. Hartge P, Schiffman MH, Hoover R, et al: A case-control study of epithelial ovarian cancer. Am J Obstet Gynecol 161:10, 1989.
96. Henderson BE, Casagrande JT, Pike MC, et al: The epidemiology of endometrial cancer in young women. Br J Cancer 47:749, 1983.
97. Hensone D, Tarone R: An epidemiologic study of cancer of the

cervix, vagina, and vulva based on the Third National Cancer Survey in the United States. Am J Obstet Gynecol 129:525, 1977.

98. Herbst AL, Anderson S, Hubby MM, et al: Risk factors for the development of diethylstilbestrol-associated clear cell adenocarcinoma: A case-control study. Am J Obstet Gynecol 154:814, 1986.

99. Herbst AL, Ulfelder H, Poskanzer DC: Adenocarcinoma of the vagina: Association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med 284:878, 1971.

100. Herman JM, Homesley HD, Dignan MB: Is hysterectomy a risk factor for vaginal cancer? JAMA 256:601, 1986.

101. Herrero R, Brinton LA, Reeves WC, et al: Sexual behavior, venereal diseases, hygiene practices, and invasive cervical cancer in a high-risk population. Cancer 65:380, 1990.

102. Hildesheim A, Brinton LA, Mallin K, et al: Barrier and spermicidal contraceptive methods and risk of invasive cervical cancer. Epidemiology 1:266, 1990.

103. Hildreth NG, Kelsey JL, LiVolsi VA, et al: An epidemiologic study of epithelial carcinoma of the ovary. Am J Epidemiol 114:398, 1981.

104. Hoover R: Effects of drugs—immunosuppression. In Hiatt HH, Watson JD, Winsten JA (eds): Origins of Human Cancer. Cold Spring Harbor Conferences on Cell Proliferation 4, pp. 369–379. New York, Cold Spring Harbor Laboratory, 1977.

105. Horwitz RI, Feinstein AR: Alternative analytic methods for case-control studies of estrogens and endometrial cancer. N Engl J Med 299:1089, 1978.

106. Horwitz RI, Feinstein AR, Horwitz SM, et al: Necropsy diagnosis of endometrial cancer and detection-bias in case-control studies. Lancet 2:66, 1981.

107. Hulka BS, Chambless LE, Kaufman DG, et al: Protection against endometrial carcinoma by combination-product oral contraceptives. JAMA 247:475, 1982.

108. Hulka BS, Fowler WC, Kaufman DG, et al: Estrogen and endometrial cancer: Cases and two control groups from North Carolina. Am J Obstet Gynecol 137:92, 1980.

109. Jimerson GK, Merrill JA: Multicentric squamous malignancy involving both cervix and vulva. Cancer 26:150, 1970.

110. Joly DJ, Lilienfeld AM, Diamond EL, et al: An epidemiologic study of the relationship of reproductive experience to cancer of the ovary. Am J Epidemiol 99:190, 1974.

111. Jones EG, Macdonald I, Breslow L: A study of epidemiologic factors in carcinoma of the uterine cervix. Am J Obstet Gynecol 76:1, 1958.

112. Kaufman DW, Kelly JP, Welch WR, et al: Noncontraceptive estrogen use and epithelial ovarian cancer. Am J Epidemiol 130:1142, 1989.

113. Kaufman DW, Shapiro S, Slone D, et al: Decreased risk of endometrial cancer among oral-contraceptive users. N Engl J Med 303:1045, 1980.

114. Kaufman RH, Dreesman GR, Burek J, et al: Herpesvirus-induced antigens in squamous-cell carcinoma in situ of the vulva. N Engl J Med 305:483, 1981.

115. Kelsey JL, Hildreth NG (eds): Breast and Gynecologic Cancer Epidemiology. Boca Raton, FL, CRC Press, 1983.

116. Kelsey JL, LiVolsi VA, Holford TR, et al: A case-control study of cancer of the endometrium. Am J Epidemiol 116:333, 1982.

117. Kessler II: Venereal factors in human cervical cancer: Evidence from marital clusters. Cancer 39:1912, 1977.

118. Kinlen LJ: Meat and fat consumption and cancer mortality: A study of strict religious orders in Britain. Lancet 1:946, 1982.

119. Kinlen LJ, Spriggs AI: Women with positive cervical smears but without surgical intervention: A follow-up study. Lancet 2:463, 1978.

120. Kirschner MA, Schneider G, Ertel NH, et al: Obesity, androgens, estrogens, and cancer risk. Cancer Res 43:3281, 1982.

121. Kjaer SK, de Villiers EM, Haugaard BJ, et al: Human papillomavirus, herpes simplex virus and cervical cancer incidence in Greenland and Denmark. A population-based cross-sectional study. Int J Cancer 41:518, 1988.

122. Koch M, Gaedke H, Jenkins H: Family history of ovarian cancer patients: A case-control study. Int J Epidemiol 18:782, 1989.

123. Koutsky LA, Galloway DA, Holmes KK: Epidemiology of genital human papillomavirus infection. Epidemiol Rev 10:122, 1988.

124. Kovi J, Tillman RL, Lee SM: Malignant transformation of condyloma acuminatum. A light microscopic and ultrastructural study. Am J Clin Pathol 61:702, 1974.

125. Kurman RJ, Jenson AB, Lancaster WD: Papillomavirus infection and squamous neoplasia of the cervix. Pathol Res Pract 179:24, 1984.

126. Kurman RJ, Schiffman MH, Lancaster WD, et al: Analysis of individual human papillomavirus types in cervical neoplasia: A possible role for type 18 in rapid progression. Am J Obstet Gynecol 159:293, 1988.

127. Lancaster WD, Castellano C, Santos C, et al: Human papillomavirus deoxyribonucleic acid in cervical carcinoma from primary and metastatic sites. Am J Obstet Gynecol 154:115, 1986.

128. La Vecchia C, Decarli A, Fasoli M, et al: Dietary vitamin A and the risk of intraepithelial and invasive neoplasia. Gynecol Oncol 30:187, 1988.

129. La Vecchia C, Decarli A, Fasoli M, et al: Nutrition and diet in the etiology of endometrial cancer. Cancer 57:1248, 1986.

130. La Vecchia C, Decarli A, Franceschi S, et al: Age at first birth and the risk of ovarian cancer. JNCI 73:663, 1984.

131. La Vecchia C, Decarli A, Negri E, et al: Dietary factors and the risk of epithelial ovarian cancer. JNCI 79:663, 1987.

132. La Vecchia C, Franceschi S, Decarli A, et al: Cigarette smoking and the risk of cervical neoplasia. Am J Epidemiol 123:22, 1986.

133. La Vecchia C, Franceschi S, Decarli A, et al: Coffee drinking and the risk of epithelial ovarian cancer. Int J Cancer 33:559, 1984.

134. La Vecchia C, Franceschi S, Decarli A, et al: "Pap" smear and the risk of cervical neoplasia. Quantitative estimates from a case-control study. Lancet 2:779, 1984.

135. La Vecchia C, Franceschi S, Decarli A, et al: Risk factors for endometrial cancer at different ages. JNCI 73:667, 1984.

136. La Vecchia C, Franceschi S, Decarli A, et al: Sexual factors, venereal diseases, and the risk of intraepithelial and invasive cervical neoplasia. Cancer 58:935, 1986.

137. La Vecchia C, Franceschi S, Parazzini F, et al: Risk factors for gestational trophoblastic disease in Italy. Am J Epidemiol 121:457, 1985.

138. La Vecchia C, Parazzini F, Decarli A, et al: Age of parents and risk of gestational trophoblastic disease. JNCI 73:639, 1984.

139. Lawrence C, Tessaro I, Durgerian S, et al: Smoking, body weight, and early-stage endometrial cancer. Cancer 49:1665, 1987.

140. Lesko SM, Rosenberg L, Kaufman DW, et al: Cigarette smoking and the risk of endometrial cancer. N Engl J Med 313:593, 1985.

141. Lorincz AT, Temple GF, Kurman RJ, et al: Oncogenic association of specified human papillomavirus types with cervical neoplasia. JNCI 79:671, 1987.

142. Mabuchi K, Bross DS, Kessler II: Epidemiology of cancer of the vulva. A case-control study. Cancer 55:1843, 1985.

143. McCance DJ, Clarkson PK, Dyson JL, et al: Human papillomavirus types 6 and 16 in multifocal intraepithelial neoplasias of the female lower genital tract. Br J Obstet Gynaecol 92:1093, 1985.

144. McCarroll AM, Montgomery DAD, Harley JM, et al: Endometrial carcinoma after cyclical oestrogen-progestogen therapy for Turner's syndrome. Br J Obstet Gynaecol 82:421, 1975.

145. Macdonald TW, Annegers JF, O'Fallon WM, et al: Exogenous estrogen and endometrial carcinoma: Case-control and incidence study. Am J Obstet Gynecol 127:572, 1977.

146. McDougall JK, Beckmann AM, Galloway DA: The enigma of viral nucleic acids in genital neoplasia. In Peto R, zur Hausen H (eds): Viral Etiology of Cervical Cancer. Banbury Report 21, pp. 199–210. New York, Cold Spring Harbor Laboratory, 1986.

147. McGowan L, Parent L, Lednar W, et al: The woman at risk for developing ovarian cancer. Gynecol Oncol 7:325, 1979.
148. Mack TM, Pike MC, Henderson BE, et al: Estrogens and endometrial cancer in a retirement community. N Engl J Med 294: 1262, 1976.
149. MacMahon B: Risk factors for endometrial cancer. Gynecol Oncol 2:122, 1974.
150. MacMahon B, Trichopoulos D, Cole P, et al: Cigarette smoking and urinary estrogens. N Engl J Med 307:1062, 1982.
151. Marshall JR, Graham S, Byers T, et al: Diet and smoking in the epidemiology of cancer of the cervix. JNCI 70:847, 1983.
152. Martin CE: Marital and coital factors in cervical cancer. Am J Public Health 57:803, 1967.
153. Martinez I: Relationship of squamous cell carcinoma of the cervix uteri to squamous cell carcinoma of the penis among Puerto Rican women married to men with penile carcinoma. Cancer 24:777, 1969.
154. Mason TJ, McKay FW, Hoover R, et al: Atlas of Cancer Mortality for U.S. Counties: 1950–1969. Bethesda, MD, DHEW Publication No. (NIH) 75–780, 1975.
155. Meanwell CA, Cox MF, Blackledge G, et al: HPV 16 DNA in normal and malignant cervical epithelium: Implications for the aetiology and behaviour of cervical neoplasia. Lancet 1:703, 1987.
156. Meisels A, Fortin R: Condylomatous lesions of the cervix and vagina. I. Cytologic patterns. Acta Cytol 20:505, 1976.
157. Menczer J, Modan M, Ranon L, et al: Possible role of mumps virus in the etiology of ovarian cancer. Cancer 43:1375, 1979.
158. Messerli ML, Lilienfeld AM, Parmley T, et al: Risk factors for gestational trophoblastic neoplasia. Am J Obstet Gynecol 153: 294, 1985.
159. Miller DR, Rosenberg L, Kaufman DW, et al: Epithelial ovarian cancer and coffee drinking. Int J Epidemiol 16:13, 1987.
160. Morrow P, Nakamura R, Schlaerth J, et al: The influence of oral contraceptives on the postmolar human chorionic gonadotropin regression curve. Am J Obstet Gynecol 151:906, 1985.
161. Muir C, Waterhouse J, Mack T, et al (eds): Cancer Incidence in Five Continents, vol V. Lyon, France, IARC Scientific Publication 88, 1987
162. Munoz N, Bosch X, Kaldor JM: Does human papillomavirus cause cervical cancer? The state of the epidemiological evidence. Br J Cancer 57:1, 1988.
163. Nachtigall LE, Nachtigall RH, Nachtigall RD, et al: Estrogen replacement therapy II: A prospective study in the relationship to carcinoma and cardiovascular and metabolic problems. Obstet Gynecol 54:74, 1979.
164. Nasca PC, Greenwald P, Chorost S, et al: An epidemiologic case-control study of ovarian cancer and reproductive factors. Am J Epidemiol 119:705, 1984.
165. National Cancer Institute Workshop: The 1988 Bethesda system for reporting cervical/vaginal cytologic diagnoses. JAMA 262: 931, 1989.
166. Newcomb PA, Weiss NS, Daling J: Incidence of vulvar carcinoma in relation to menstrual, reproductive, and medical factors. JNCI 73:391, 1984.
167. Noller KL, Decker DG, Lanier AP, et al: Clear-cell adenocarcinoma of the cervix after maternal treatment with synthetic estrogens. Proc Staff Meet Mayo Clin 47:629, 1972.
168. Okagaki T. Female genital tumors associated with human papillomavirus infection, and the concept of genital neoplasms-papilloma syndrome (GENPS). Pathol Annu 19:31, 1984.
169. Olesen F: A case-control study of cervical cytology before diagnosis of cervical cancer in Denmark. Int J Epidemiol 17:501, 1988.
170. Parazzini F, La Vecchia C, Franceschi S, et al: ABO blood groups and the risk of gestational trophoblastic disease. Tumori 71:123, 1985.
171. Parazzini F, La Vecchia C, Negri E, et al: Reproductive factors and the risk of invasive and intraepithelial cervical neoplasia. Br J Cancer 59:805, 1989.
172. Parazzini F, La Vecchia C, Pampallona S, et al: Reproductive patterns and the risk of gestational trophoblastic disease. Am J Obstet Gynecol 152:866, 1985.
173. Paterson MEL, Wade-Evans T, Sturdee DW, et al: Endometrial disease after treatment with oestrogen and progestogens in the climacteric. Br Med J 280:822, 1980.
174. Persky V, Davis F, Barrett R, et al: Recent time trends in uterine cancer. Am J Public Health 80:935, 1990.
175. Persson I, Adami HO, Bergkvist L, et al: Risk of endometrial cancer after treatment with oestrogens alone or in conjunction with progestogens: Results of a prospective study. Br Med J 298:147, 1989.
176. Peterson O: Spontaneous course of cervical precancerous conditions. Am J Obstet Gynecol 72:1063, 1956.
177. Phillips RL, Garfinkel L, Kuzma JW, et al: Mortality among California Seventh-Day Adventists for selected cancer sites. JNCI 65:1097, 1980.
178. Piper JM: Oral contraceptives and cervical cancer. Gynecol Oncol 22:1, 1985.
179. Reeves WC, Brinton LA, Garcia M, et al: Human papillomavirus (HPV) infection and cervical cancer in Latin America. N Engl J Med 320:1437, 1989.
180. Reeves WC, Rawls WE, Brinton LA: Epidemiology of genital papillomaviruses and cervical cancer. Rev Infect Dis 11:426, 1989.
181. Rice JM, Williams GM, Palmer AE, et al: Pathology of gestational choriocarcinoma induced in patas monkeys by ethylnitrosourea given during pregnancy. Placenta (suppl 3):223, 1981.
182. Richart RM, Baron BA: A follow-up study of patients with cervical dysplasia. Am J Obstet Gynecol 105:386, 1969.
183. Risch HA, Weiss NS, Lyon JL, et al: Events of reproductive life and the incidence of epithelial ovarian cancer. Am J Epidemiol 117:128, 1983.
184. Romney SL, Duttagupta C, Basu J, et al: Plasma vitamin C and uterine cervical dysplasia. Am J Obstet Gynecol 151:976, 1985.
185. Rose DP, Boyar AP: Diet and ovarian cancer. JAMA 254:2553, 1985.
186. Rose PG, Herterick EE, Boutselis JG, et al: Multiple primary gynecologic neoplasms. Am J Obstet Gynecol 157:261, 1987.
187. Rosenberg L, Palmer JR, Shapiro S: Gestational trophoblastic disease and use of oral contraceptives. [Letter] Am J Obstet Gynecol 161:1087, 1989.
188. Rosenberg L, Shapiro S, Slone D, et al: Epithelial ovarian cancer and combination oral contraceptives. JAMA 247:3210, 1982.
189. Rotkin ID: Adolescent coitus and cervical cancer: Associations of related events with increased risk. Cancer Res 27:603, 1967.
190. Rubin GL, Peterson HB, Lee NC, et al: Estrogen replacement therapy and the risk of endometrial cancer: Remaining controversies. Am J Obstet Gynecol 162:148, 1990.
191. Rutledge F: Cancer of the vagina. Am J Obstet Gynecol 97:635, 1967.
192. Schachter J, Hill EC, King EB, et al: Chlamydia trachomatis and cervical neoplasia. JAMA 248:2134, 1982.
193. Schiffman MH, Haley NJ, Felton JS, et al: Biochemical epidemiology of cervical neoplasia: Measuring cigarette smoke constituents in the cervix. Cancer Res 47:3886, 1987.
194. Schiffman MH, Hartge P, Lesher LP, et al: Mumps and postmenopausal ovarian cancer. [Letter] Am J Obstet Gynecol 152:116, 1985.
195. Schildkraut JM, Thompson WD: Familial ovarian cancer: A population-based case-control study. Am J Epidemiol 128:456, 1988.
196. Schmauz R, Okong P, de Villiers EM, et al: Multiple infections in cases of cervical cancer from a high-incidence area in tropical Africa. Int J Cancer 43:805, 1989.

197. Schneider A, Hotz M, Gissmann L: Increased prevalence of human papillomaviruses in the lower genital tract of pregnant women. Int J Cancer 40: 198, 1987.

198. Schneider V, Kay S, Lee HM: Immunosuppression as a high-risk factor in the development of condyloma acuminatum and squamous neoplasia of the cervix. Act Cytol 27: 220, 1983.

199. Schwartz SM, Weiss NS: Increased incidence of adenocarcinoma of the cervix in young women in the United States. Am J Epidemiol 124: 1045, 1986.

200. Shapiro S, Kelly JP, Rosenberg L, et al: Risk of localized and widespread endometrial cancer in relation to recent and discontinued use of conjugated estrogens. N Engl J Med 313: 969, 1985.

201. Shu XO, Gao YT, Yuan JM, et al: Dietary factors and epithelial ovarian cancer. Br J Cancer 59: 92, 1989.

202. Siiteri PK: Steroid hormones and endometrial cancer. Cancer Res 38: 4360, 1978.

203. Silverberg SG, Mullen D, Faraci JA, et al: Endometrial carcinoma: Clinical-pathologic comparison of cases in postmenopausal women receiving and not receiving exogenous estrogens. Cancer 45: 3018, 1980.

204. Slattery ML, Abbott TM, Overall JC Jr, et al: Dietary vitamins A, C, and E and selenium as risk factors for cervical cancer. Epidemiology 1: 8, 1990.

205. Slattery ML, Overall JC Jr, Abbott TM, et al: Sexual activity, contraception, genital infections, and cervical cancer: Support for a sexually transmitted disease hypothesis. Am J Epidemiol 130: 248, 1989.

206. Slattery ML, Robison LM, Schuman KL, et al: Cigarette smoking and exposure to passive smoke are risk factors for cervical cancer. JAMA 261: 1593, 1989.

207. Slattery ML, Schuman KL, West DW, et al: Nutrient intake and ovarian cancer. Am J Epidemiol 130: 497, 1989.

208. Smith DC, Prentice R, Thompson DJ, et al: Association of exogenous estrogen and endometrial carcinoma. N Engl J Med 293: 1164, 1975.

209. Smith EM, Sowers MF, Burns TL: Effects of smoking on the development of female reproductive cancers. JNCI 73: 371, 1984.

210. Smith PG, Kinlen LJ, White GC, et al: Mortality of wives of men dying with cancer of the penis. Br J Cancer 41: 442, 1980.

211. Snowdon DA: Diet and ovarian cancer. JAMA 254: 356, 1985.

212. Stadel BV: The etiology and prevention of ovarian cancer. Am J Obstet Gynecol 123: 772, 1975.

213. Stern E, Neely PM: Carcinoma and dysplasia of the cervix: A comparison of rates for new and returning populations. Acta Cytol 7: 357, 1963.

214. Stockwell HG, Lyman GH: Cigarette smoking and the risk of female reproductive cancer. Am J Obstet Gynecol 157: 35, 1987.

215. Stone M, Dent J, Kardana A, et al: Relationship of oral contraception to development of trophoblastic tumour after evacuation of a hydatidiform mole. Br J Obstet Gynaecol 83: 913, 1976.

216. Stuart GC, Allen HH, Anderson RJ: Squamous cell carcinoma of the vagina following hysterectomy. Am J Obstet Gynecol 139: 311, 1981.

217. Teoh ES, Dawood MY, Ratnam SS: Observations on choriocarcinoma in Singapore. Obstet Gynecol 40: 519, 1972.

218. Terris M, Wilson F, Smith H, et al: The relationship of coitus to carcinoma of the cervix. Am J Public Health 57: 840, 1967.

219. Trichopoulos D, Papapostolou M, Polychronopoulou A: Coffee and ovarian cancer. Int J Cancer 28: 691, 1981.

220. Tyler CW Jr, Webster LA, Ory HW, et al: Endometrial cancer: How does cigarette smoking influence the risk of women under age 55 years having this tumor? Am J Obstet Gynecol 151: 899, 1985.

221. Vermund SH, Schiffman MH, Golberg GL, et al: Molecular diagnosis of genital human papillomavirus infection: Comparison of two methods used to collect exfoliated cervical cells. Am J Obstet Gynecol 160: 304, 1989.

222. Verreault R, Chu J, Mandelson M, et al: A case-control study of diet and invasive cervical cancer. Int J Cancer 43: 1050, 1989.

223. Villa LL, Franco ELF: Epidemiologic correlates of cervical neoplasia and risk of human papillomavirus infection in asymptomatic women in Brazil. JNCI 81: 332, 1989.

224. Voigt LF, Harlow BL, Weiss NS: The influence of age at first birth and parity on ovarian cancer risk. Am J Epidemiol 124: 490, 1986.

225. Vonka V, Kanka J, Hirsch I, et al: Prospective study on the relationship between cervical neoplasia and herpes simplex type-2 virus. II. Herpes simplex type-2 antibody presence in sera taken at enrollment. Int J Cancer 33: 61, 1984.

226. Walker AM, Jick H: Declining rates of endometrial cancer. Obstet Gynecol 56: 733, 1980.

227. Wassertheil-Smoller S, Romney SL, Wylie-Rosett J, et al: Dietary vitamin C and uterine cervical dysplasia. Am J Epidemiol 114: 714, 1981.

228. Webster LA, Weiss NS, the Cancer and Steroid Hormone Study Group: Alcoholic beverage consumption and the risk of endometrial cancer. Int J Epidemiol 18: 786, 1989.

229. Weiss NS, Harlow BL: Why does hysterectomy without bilateral oophorectomy influence the subsequent incidence of ovarian cancer? Am J Epidemiol 124: 856, 1986.

230. Weiss NS, Lyon JL, Krishnamurthy S, et al: Non-contraceptive estrogen use and the occurrence of ovarian cancer. JNCI 68: 95, 1982.

231. Weiss NS, Lyon JL, Liff JM, et al: Incidence of ovarian cancer in relation to the use of oral contraceptives. Int J Cancer 28: 669, 1981.

232. Weiss NS, Sayvetz TA: Incidence of endometrial cancer in relation to the use of oral contraceptives. N Engl J Med 302: 551, 1980.

233. Weiss NS, Szekely DR, Austin DF: Increasing incidence of endometrial cancer in the United States. N Engl J Med 294: 1259, 1976.

234. Weiss NS, Szekely DR, English DR, et al: Endometrial cancer in relation to patterns of menopausal estrogen use. JAMA 242: 261, 1979.

235. Whitehead MI, Townsend PT, Pryse-Davies J, et al: Effects of estrogens and progestins on the biochemistry and morphology of the postmenopausal endometrium. N Engl J Med 305: 1599, 1981.

236. Whitehead N, Reyner F, Lindenbaum J: Megaloblastic changes in the cervical epithelium: Association with oral contraceptive therapy and reversal with folic acid. JAMA 226: 1421, 1973.

237. Whittemore AS, Wu ML, Paffenbarger RS, et al: Epithelial ovarian cancer and the ability to conceive. Cancer Res 49: 4047, 1989.

238. Whittemore AS, Wu ML, Paffenbarger RS, et al: Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol and coffee. Am J Epidemiol 128: 1228, 1988.

239. Wilkinson EJ, Friedrich EG, Mattingly RF, et al: Turner's syndrome with endometrial adenocarcinoma and silbestrol therapy. Obstet Gynecol 42: 193, 1973.

240. WHO Collaborative Study of Neoplasia and Steroid Contraceptives: Epithelial ovarian cancer and combined oral contraceptives. Int J Epidemiol 18: 538, 1989.

241. WHO Collaborative Study of Neoplasia and Steroid Contraceptives: Invasive cervical cancer and combined oral contraceptives. Br Med J 290: 961, 1985.

242. Winkelstein W Jr: Smoking and cervical cancer—current status: A review. Am J Epidemiol 131: 945, 1990.

243. Wright NH, Vessey MP, Kenward B, et al: Neoplasia and dysplasia of the cervix uteri and contraception: A possible protective effect of the diaphragm. Br J Cancer 38: 273, 1978.

244. Wu ML, Whittemore AS, Paffenbarger RS, Jr, et al: Personal and environmental characteristics related to epithelial ovarian cancer. I. Reproductive and menstrual events and oral contraceptive use. Am J Epidemiol 128: 1216, 1988.

245. Wynder EL, Escher GC, Mantel N: An epidemiological investigation of cancer of the endometrium. Cancer 19:489, 1966.
246. Yuen BH, Burch P: Relationship of oral contraceptives and the intrauterine contraceptive devices to the regression of concentrations of the beta subunit of human chorionic gonadotropin and invasive complications after molar pregnancy. Am J Obstet Gynecol 145:214, 1983.
247. Zajicek J: Ovarian cystomas and ovulation, a histogenetic concept. Tumori 63:429, 1977.
248. Ziegler RG, Brinton LA, Hamman RF, et al: Diet and the risk of invasive cervical cancer among white women in the United States. Am J Epidemiol 132:432, 1990.
249. Ziegler RG, Jones CJ, Brinton LA, et al: Diet and the risk of in situ cervical cancer among white women in the United States. Cancer Causes Control 2:17, 1991.
250. Zunzunegui MV, King MC, Coria CF, et al: Male influences on cervical cancer risk. Am J Epidemiol 123:302, 1986.
251. Zur Hausen H: Human genital cancer: Synergism between two virus infections or synergis between a virus infection and initiating event? Lancet 2:1370, 1982.